PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classificati n 6 :
C07D 277/28, 277/30, A61K 31/425, C07D 277/56, 277/24

A1

(11) International Publication Number: WO 96/33181

(43) Internati nal Publication Date: 24 October 1996 (24.10.96)

(21) International Application Number: PCT/JP96/01079

(22) International Filing Date: 19 April 1996 (19.04.96)

(30) Priority Data:
7/97002 21 April 1995 (21.04.95) JP

(71) Applicant (*for all designated States except US*): DAIICHI PHARMACEUTICAL CO., LTD. [JP/JP]; 14-10, Nihonbashi 3-chome, Chuo-ku, Tokyo 103 (JP).

(72) Inventors; and

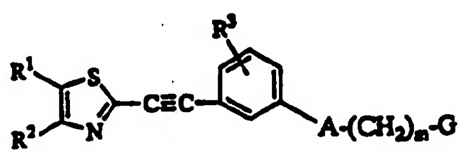
(75) Inventors/Applicants (*for US only*): NAKAYAMA, Atsushi [JP/JP]; Daiichi Pharmaceutical Co., Ltd. Tokyo R & D Center, 16-13, Kita-Kasai 1-chome, Edogawa-ku, Tokyo 134 (JP). MACHINAGA, Nobuo [JP/JP]; Daiichi Pharmaceutical Co., Ltd. Tokyo R & D Center, 16-13, Kita-Kasai 1-chome, Edogawa-ku, Tokyo 134 (JP). YAMAGUCHI, Hitoshi [JP/JP]; Daiichi Pharmaceutical Co., Ltd. Tokyo R & D Center, 16-13, Kita-Kasai 1-chome, Edogawa-ku, Tokyo 134 (JP). TAKEDA, Toshiyuki [JP/JP]; Daiichi Pharmaceutical Co., Ltd. Tokyo R & D Center, 16-13, Kita-Kasai 1-chome, Edogawa-ku, Tokyo 134 (JP). HARUTA, Makoto [JP/JP]; Daiichi Pharmaceutical Co., Ltd. Tokyo R & D Center, 16-13, Kita-Kasai 1-chome, Edogawa-ku, Tokyo 134 (JP). OGASAWARA, Tomomi [JP/JP]; Daiichi Pharmaceutical Co., Ltd. Tokyo R & D Center, 16-13, Kita-Kasai 1-chome, Edogawa-ku, Tokyo 134 (JP). MATSUMURA, Manabu [JP/JP]; Daiichi Pharmaceutical Co., Ltd. Tokyo R & D Center, 16-13, Kita-Kasai 1-chome, Edogawa-ku, Tokyo 134 (JP).

(74) Agents: HAGINO, Taira et al.; Eikoh Patent Office, ARK Mori Building, 28th floor, 12-32, Akasaka 1-chome, Minato-ku, Tokyo 107 (JP).

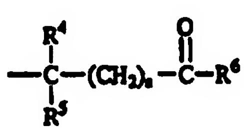
(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

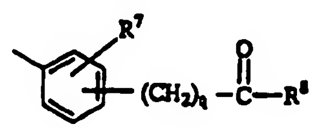
(54) Title: ETHYNYLTHIAZOLE DERIVATIVE



(1)



(2)



(3)

(57) Abstract

An ethynylthiazole derivative represented by formula (1), wherein R^1 and R^2 independently represent a hydrogen atom, a halogen atom, an alkyl group which may have a substituent or a cycloalkyl group which may have a substituent, or R^1 and R^2 may together form a ring; R^3 represents a hydrogen atom, a hydroxyl group, a halogen atom, an alkyl group which may have a substituent, an alkoxyl group which may have a substituent, a carboxyl group or an alkoxycarbonyl group which may have a substituent; A represents a group -NHCO-, a group -CONH- or a group $-NHSO_2-$; m is an integer of 0 to 3; and G is a group represented by formula (2) or (3), wherein R^4 and R^5 independently represent a hydrogen atom or an alkyl group which may have a substituent, or R^4 and R^5 may together form a ring; n is an integer of 0 or 1; and R^6 represents a hydroxyl group or an alkoxyl group which may have a substituent, or formula (3), wherein R^7 represents a hydrogen atom, a hydroxyl group, a halogen atom, an alkyl group which may have a substituent, an alk xyl group which may have a substituent, a cyano group, a nitro group, a carboxyl group or an alkoxycarbonyl group which may have a substituent; q is an integer of 0 or 1; and R^8 represents a hydroxyl group or an alkoxyl group which may have a substituent; and an allergic disease treating agent which contains the derivative as its active ingredient.

DESCRIPTION

ETHYNYLTHIAZOLE DERIVATIVE

TECHNICAL FIELD

This invention relates to an ethynylthiazole derivative and to a drug treating allergic diseases which contains the derivative as an active ingredient.

BACKGROUND ART

Peptide leukotrienes are an inflammatory mediator which is produced in living systems from arachidonic acid, and leukotriene C_4 (LTC_4), leukotriene D_4 (LTD_4) and leukotriene E_4 (LTE_4) are known as the peptide leukotrienes (*Science*, 220: 568 - 575, 1983). These compounds are regarded as one of the main mediators which induce bronchial asthma in human (*Proc. Natl. Acad. Sci. USA*, 80: 1712 - 1716, 1983).

On the other hand, from the viewpoint of developing drugs for use in the treatment of allergic diseases typically including bronchial asthma, extensive studies have been carried out on the creation of substances (receptor antagonists) which antagonize leukotrienes in a competitive manner. There are many reports on leukotriene antagonists which are classified into the following several types of derivatives based on their structures (*Chimia*, 46: 304 - 311, 1992). Compounds classified as thiazole-derivatives include (i) (E)-4-[[3-[2-(4-isopropyl-2-thiazolyl)ethenyl]phenyl]amino]-2,2-diethyl-4-oxobutyric acid (Japanese Patent Publication No. 5-7386), (ii) (E)-4-[[3-[2-(4-

cyclobutyl-2-thiazolyl)eth nyl]phenyl]amino]-2,2-diethyl-4-oxobutyric acid (Japanese Patent Application (OPI) No. 2-69468 (the term "OPI" as used herein refers to a "published unexamined Japanese patent application")) and (iii) (E)-2-[2-[3-[2-(4-cyclobutyl-2-thiazolyl)ethenyl]phenylamino]-2-oxo-ethyl]benzoic acid (Japanese Patent Application (OPI) No. 6-80654). A common structural characteristic to these compounds is that the thiazole ring and the benzene ring form a trans configuration (E form in this case) through a double bond, which is an important structural feature for the expression of potent antagonism.

On the other hand, these thiazole-derivatives also have a geometrical isomer Z form (thiazole ring and benzene ring in cis configuration) in addition to the aforementioned E form (thiazole ring and benzene ring in trans configuration).

It is known that the trans form compound (ii) (E)-4-[[3-[2-(4-cyclobutyl-2-thiazolyl)ethenyl]phenyl]amino]-2,2-diethyl-4-oxobutyric acid ("Ro 24-5913" as described in Japanese Patent Application (OPI) No. 2-69468) is easily isomerized into its cis isomer (iv) (Z)-4-[[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenyl]amino]-2,2-diethyl-4-oxobutyric acid when exposed to light (*J. Pharmaceutical & Biomedical Analysis*, 11(10): 1037, 1993). It is known also that, in a compound having another chemical structure, leukotriene antagonism in its cis form is approximately 1/100 or less of its trans form (*J. Med. Chem.*, 35: 3832 - 3844, 1992).

It is assumed on the basis of these facts that, in th leukotriene antagonism of thiazole-derivativ s, antagonistic activity of the cis form is considerably reduced in comparison with the trans form, due to a difference in the leukotriene receptor-binding affinity between trans form compounds and cis form compounds.

There are many cases to develop a medicine composed of the one of geometrical isomers on the basis of the superiority of its biological activity. However, when the compound is unstable or easily isomerized into the inactive other isomer, serious problems will be caused.

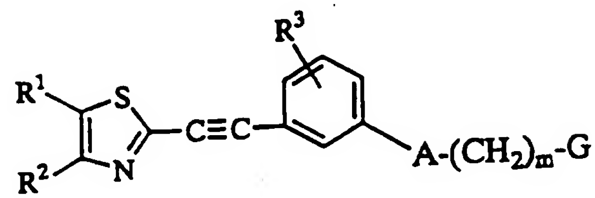
DISCLOSURE OF THE INVENTION

In order to overcome the aforementioned problems caused by the existence of geometrical isomers, the present invention contemplates obtaining a compound which is not converted easily into other isomer by light and the like, and exerts potent leukotriene antagonism.

As a result of extensive investigation to achieve the above objects, the inventors of the present invention have resolved the double bond-caused problems by employing a triple bond. Illustratively, the present invention has been accomplished through the synthesis of compounds having intramolecular triple bond, thereby resolving these problems and finding ethynylthiazole compounds which exerts potent leukotriene antagonism at the same time.

(1) The present invention relates to a compound

represented by the following formula (1) or a salt thereof:



(1)

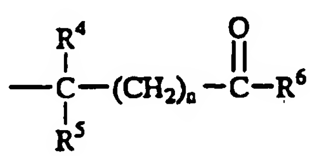
wherein R^1 and R^2 independently represent a hydrogen atom, a halogen atom, an alkyl group which may have a substituent or a cycloalkyl group which may have a substituent, or R^1 and R^2 may together form a ring;

R^3 represents a hydrogen atom, a hydroxyl group, a halogen atom, an alkyl group which may have a substituent, an alkoxyl group which may have a substituent, a carboxyl group or an alkoxycarbonyl group which may have a substituent;

A represents a group -NHCO-, a group -CONH- or a group $-NHSO_2-$;

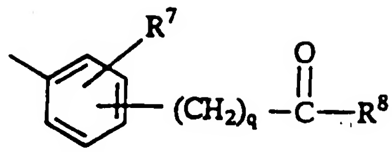
m is an integer of 0 to 3; and

G is a group represented by the following formula (2) or (3):



(2)

(wherein R^4 and R^5 independently represent a hydrogen atom or an alkyl group which may have a substituent, or R^4 and R^5 may together form a ring; n is an integer of 0 or 1; and R^6 represents a hydroxyl group or an alkoxyl group which may have a substituent), or



(3)

(wherein R^7 represents a hydrogen atom, a hydroxyl group, a halogen atom, an alkyl group which may have a substituent group, an alkoxyl group which may have a substituent, a cyano group, a nitro group, a carboxyl group or an alkoxycarbonyl group which may have a substituent; q is an integer of 0 or 1; and R^8 represents a hydroxyl group or an alkoxyl group which may have a substituent).

(2) Further, the present invention relates to the compound or a salt thereof described in the above (1), wherein R^2 in the formula (1) is an alkyl group which may have a substituent or a cycloalkyl group which may have a substituent.

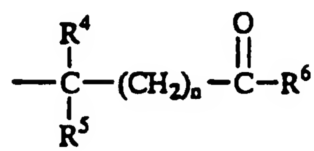
(3) Further, the present invention relates to the compound or a salt thereof described in the above (1) or (2), wherein R^1 in the formula (1) is a hydrogen atom.

(4) Further, the present invention relates to the compound or a salt thereof described in any one of the above (1) to (3), wherein R^3 in the formula (1) is a hydrogen atom.

(5) Further, the present invention relates to the compound or a salt thereof described in any one of the above (1) to (4), wherein A in the formula (1) is a group -NHCO-.

(6) Further, the present invention relates to the compound or a salt thereof described in any one of the above (1) to (5), wherein m in the formula (1) is 1.

(7) Further, the present invention relates to the compound or a salt thereof d scribed in any one of the above (1) to (6), wherein G in the formula (1) is a group represented by formula (2):



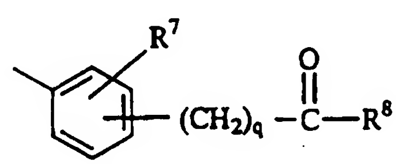
(2)

wherein R^4, R^5, R^6 and n are as defined in the foregoing.

(8) Further, the present invention relates to the compound or a salt thereof described in the above (7), wherein R^4 and R^5 in the formula (2) may be the same or different and each represents a hydrogen atom or an alkyl group having 1 to 5 carbon atoms which may have a substituent.

(9) Further, the present invention relates to the compound or a salt thereof described in the above (7) or (8), wherein n in the formula (2) is 0 and R^6 therein is a hydroxyl group.

(10) Further, the present invention relates to the compound or a salt thereof described in any one of the above (1) to (6), wherein G in the formula (1) is a group represented by formula (3):



(3)

wherein R^7, R^8 and q are as defined in the foregoing.

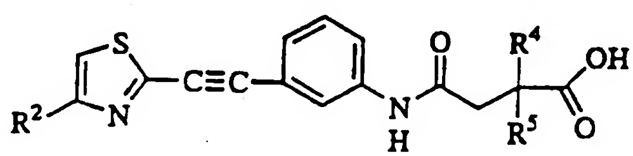
(11) Further, the present invention relates to the

compound or a salt thereof d scribed in the above (10), wherein R^7 in the formula (3) is a hydrogen atom.

(12) Further, the present invention relates to the compound or a salt thereof described in the above (10) or (11), wherein the group $-(CH_2)_q-CO-R^8$ in the formula (3) is linked to the ortho position of the phenyl group.

(13) Further, the present invention relates to the compound or a salt thereof described in any one of the above (10) to (12), wherein R^8 in the formula (3) is a hydroxyl group.

(14) Further, the present invention relates to a compound represented by formula (4) or a salt thereof:

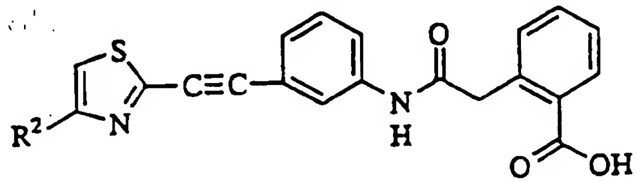


(4)

wherein R^2 represents an alkyl group which may have a substituent or a cycloalkyl group which may have a substituent, and R^4 and R^5 may be the same or different and each represents a hydrogen atom or an alkyl group having 1 to 3 carbon atoms which may have a substituent.

(15) Further, the present invention relates to the compound or a salt thereof described in any one of the above (1) to (9) and (14), which is two optical isomers which exist when R^4 and R^5 in the formula (2) are different from each other.

(16) Further, the present invention relat s to a compound represented by th following formula (5) or a salt thereof:



(5)

wherein R^2 represents an alkyl group which may have a substituent or a cycloalkyl group which may have a substituent.

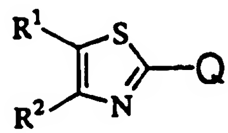
(17) Further, the present invention relates to 4-[[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenyl]amino]-2,2-diethyl-4-oxobutyric acid and 4-[[3-[2-(4-isopropyl-2-thiazolyl)-ethynyl]phenyl]amino]-2,2-diethyl-4-oxobutyric acid, or a salt thereof.

(18) Further, the present invention relates to 2-[2-[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenylamino]-2-oxoethyl]-benzoic acid and 2-[2-[3-[2-(4-isopropyl-2-thiazolyl)ethynyl]-phenylamino]-2-oxoethyl]benzoic acid, or a salt thereof.

(19) Further, the present invention relates to a compound selected from the group consisting of 2-[[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenylamino]carbonyl]benzoic acid, 2-[[[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenyl]-carbonyl]amino]benzoic acid and 4-[[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenylamino]sulfonyl]benzoic acid, or a salt thereof.

(20) Further, the present invention relates to a

compound represented by formula (6):



(6)

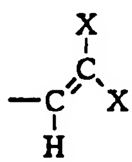
wherein R^1 and R^2 are as defined in the foregoing, and

Q is a group represented by any one of the following formulae (7) to (14):

$-CO_2Et$ (7),

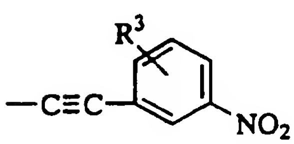
$-CH_2OH$ (8),

-CHO (9),

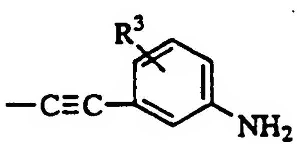


(10),

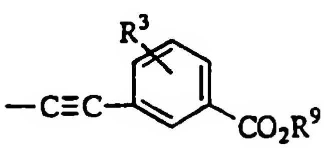
-C≡C-H (11),



(12),



(13), and



(14)

wherein X represents a halogen atom other than fluorine, R^3 is

as defined in the foregoing, and R^9 represents a hydrogen atom or an alkyl group which may have a substituent.

(21) Further, the present invention relates to an allergic disease treating drug which contains as its active ingredient the compound of any one of the above (1) to (19) or a salt thereof.

(22) Further, the present invention relates to a leukotriene antagonist which contains as its active ingredient the compound of any one of the above (1) to (19) or a salt thereof.

Substituents of the compound of the present invention represented by the formula (1) are described in the following.

The term "alkyl group" as used herein means a straight- or branched-chain saturated hydrocarbon having 1 to 7 carbon atoms, preferably a straight- or branched-chain alkyl group having 1 to 5 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl or the like group.

The term "cycloalkyl group" means a cycloalkyl group having 3 to 8 carbon atoms, preferably a cycloalkyl group having 3 to 5 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl or the like group.

The term "halogen atom" means a chlorine atom, a bromine atom, an iodine atom or a fluorine atom.

The term "alkoxyl group" means a group whose alkyl group moiety is as described above, such as methoxy, ethoxy, n-

propoxy, isopropoxy, butoxy or the like group.

The following describes the substituents R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9, m, n and q of the compound of the present invention.

Firstly, R^1 and R^2 are described.

The groups R^1 and R^2 may be the same or different from each other and each represents a hydrogen atom, a halogen atom, an alkyl group which may have a substituent, a cycloalkyl group which may have a substituent, a carboxyl group, an alkoxycarbonyl group which may have a substituent or a ring formed from R^1 and R^2.

The just described halogen atom means a fluorine atom a chlorine atom, a bromine atom or an iodine atom.

The alkyl group which may have a substituent means a straight- or branched-chain saturated hydrocarbon having 1 to 7 carbon atoms, preferably an alkyl group having 1 to 5 carbon atoms which may have a substituent, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pentyl or the like group. Examples of substituents which bind to the above alkyl groups include a halogen atom, a phenyl group, a methoxyphenyl group, a halogenophenyl group, a benzyl group, a methoxybenzyl group, a dimethoxybenzyl group, a halogenobenzyl group and the like. Chlorophenyl may be used as the halogenophenyl group, and chlorobenzyl as the halogenobenzyl group.

The cycloalkyl group which may have a substituent means a cycloalkyl group having 3 to 8 carbon atoms which may have a

substituent, preferably a cycloalkyl group having 3 to 5 carbon atoms which may have a substituent, such as cyclopropyl, cyclobutyl, cyclopentyl or the like group. Examples of substituents which bind to the above cycloalkyl groups include a halogen atom and the like.

Examples of the substituent of alkoxycarbonyl group which may have a substituent include a substituted phenyl group, a substituted benzyl group, a halogen atom and the like.

Examples of the alkoxycarbonyl group include methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl and amyloxycarbonyl.

Examples of the alkoxyl group having a substituent include a phenyl group which may have a halogen atom or a substituent and a benzyl group which may have a substituent. Examples of the phenyl group which may have a substituent include methoxyphenyl, ethoxyphenyl, chlorophenyl, trichlorophenyl, nitrophenyl and the like groups. Examples of the benzyl group which may have a substituent include methoxybenzyl, ethoxybenzyl, dimethoxybenzyl, nitrobenzyl and the like groups.

The ring which is formed by R^1 and R^2 means a ring having 5 to 8 carbon atoms, preferably a ring having 6 or 7 carbon atoms, such as cyclohexane, benzene, cycloheptane and the like rings which may have a substituent.

With regard to preferred examples of R^1 and R^2, a hydrogen atom is desirable as R^1 and an alkyl group which may

have a substituent and a cycloalkyl group which may have a substituent are desirable as R^2.

Next, R^3 is described.

The group R^3 means a hydrogen atom, a hydroxyl group, a halogen atom, an alkyl group which may have a substituent, an alkoxyl group which may have a substituent, carboxyl group or an alkoxycarbonyl group which may have a substituent.

Examples of the alkoxyl group which may have a substituent include methoxy, ethoxy, n-propoxy, isopropoxy, butoxy and the like groups. Examples of the alkoxyl group having an substituent include a trifluoromethoxy group and the like.

Examples of the group which binds to the alkoxyl group or binds to the alkoxycarbonyl group include a halogen atom and a phenyl group which may have a substituent. Examples of the phenyl group which may have a substituent include phenyl, methoxyphenyl, a halogenophenyl and the like groups.

Of the above examples, a hydrogen atom is preferable as R^3.

Next, R^4 and R^5 are described.

The groups R^4 and R^5 independently mean a hydrogen atom or an alkyl group which may have a substituent, and the alkyl group which may have a substituent has the same meaning as described in the foregoing.

The ring which is formed by R^4 and R^5 means a ring

having 3 to 8 carbon atoms, pr ferably a ring having 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclop ntyl, cyclohexyl and the like cycloalkyl groups.

Next, R^6 and R^8 are described.

The groups R^6 and R^8 may be the same or different from each other and each means hydroxyl group or an alkoxy group which may have a substituent, and hydroxyl group is preferable as R^6 and R^8.

Next, R^7 is described.

The group R^7 means a hydrogen atom, a hydroxyl group, a halogen atom, an alkyl group which may have a substituent, an alkoxyl group which may have a substituent, a cyano group, a nitro group, a carboxyl group or an alkoxycarbonyl group which may have a substituent.

Of these groups, a hydrogen atom is preferred as R^7.

Next, A is described.

The group A means a group -NHCO-, a group -CONH- or a group $-NHSO_2-$. Of these, the group -NHCO- is preferred as A.

Next, m, n and q are described.

The symbol m means an integer of 0 to 3, of which 1 is desirable as m.

The symbol n means an integer of 0 or 1, of which 0 is desirable as n.

The symbol q means an integer of 0 or 1, of which 0 is desirable as q.

In the compound of formula (1), R^1 is pr ferably a hydrogen atom and, in that case, R^2 is preferably an alkyl group which may have a substituent or a cycloalkyl group which may have a substituent.

Next, R^9 is described.

The group R^9 means a hydrogen atom or an alkyl group which may have a substituent.

Next, combination of substituents is described.

A case in which G is the formula (2) is as follows.

In this case, it is preferable that R^4 and R^5 are the same or different from each other and each is a hydrogen atom or an alkyl group having 1 to 5 carbon atoms. The alkyl group in that case is preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, pentyl or the like group.

The integer n is preferably 0, and R^6 is preferably a hydroxyl group.

A case in which G is the formula (3) is as follows.

The group $-(CH_2)_q-CO-R^8$ in the formula (3) is preferably bonded at the ortho position, and, in that case, q is preferably 0 and R^8 is preferably a hydroxyl group.

Typical examples of the compound of the present invention include 4-[[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]-phenyl]amino]-2,2-diethyl-4-oxobutyric acid,

4-[[3-[2-(4-isopropyl-2-thiazolyl)ethynyl]phenyl]amino]-2,2-diethyl-4-oxobutyric acid,

2-[2-[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenylamino]-2-oxoethyl]benzoic acid,

2-[2-[3-[2-(4-isopropyl-2-thiazolyl)ethynyl]phenylamino]-2-oxoethyl]benzoic acid,

2-[[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenylamino]-carbonyl]benzoic acid,

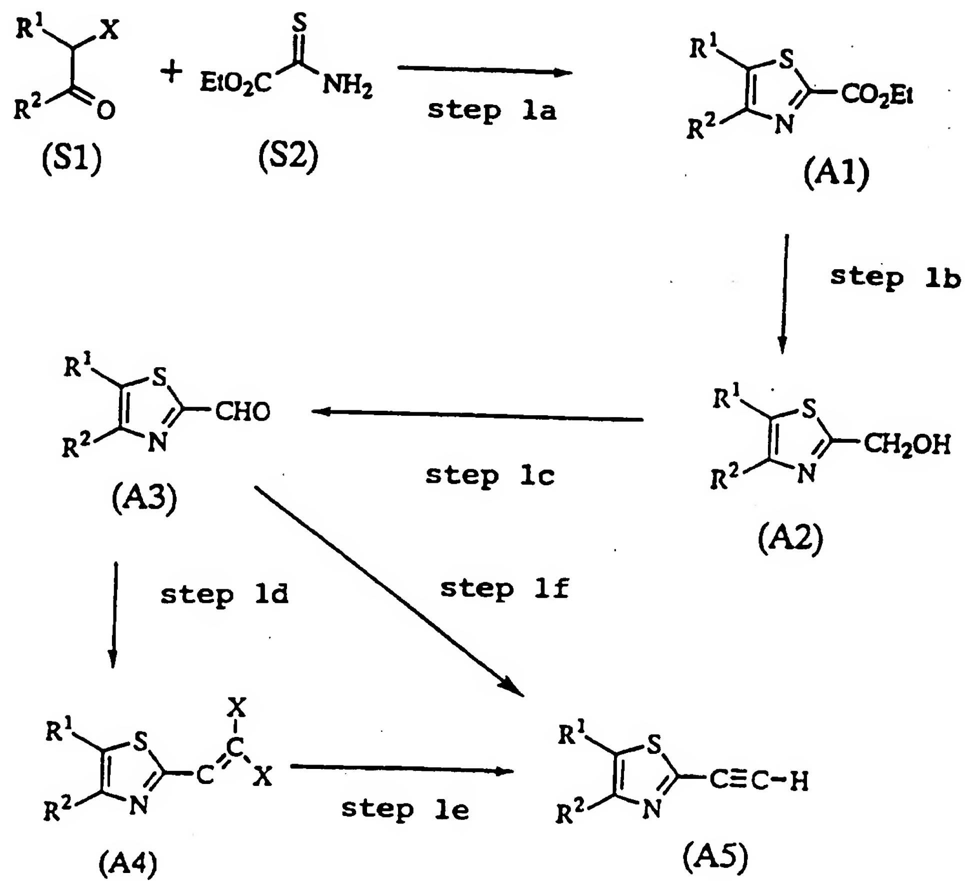
2-[[[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenyl]carbonyl]-amino]benzoic acid, and

4-[[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenylamino]-sulfonyl]benzoic acid.

The following describes production process of the compound of the present invention.

The compound of the present invention represented by the formula (1) can be synthesized in accordance with the reaction methods (1) to (9) illustrated below. These methods are described in order.

Reaction 1


R1
X
R2
O
(S1)
+
S
EtO2C
NH2
(S2)
step 1a
R1
S
CO2Et
R2
N
(A1)
step 1b
R1
S
CHO
R2
N
(A3)
step 1c
R1
S
CH2OH
R2
N
(A2)
step 1d
step 1f
R1
S
X
C
C
X
R2
N
(A4)
step 1e
R1
S
C≡C-H
R2
N
(A5)

As displayed by the step 1a, a compound represented by the formula (A1) can be obtained by allowing a compound (S1) to react with a compound (S2). In this case, the compound (S1) is α-bromoketone, α-chloroketone and the like haloketones which are commercially available known compounds or can be produced by known techniques.

The compound represented by the formula (A1) such as ethyl 4-cyclobutyl-2-thiazolecarboxylate or a 2-thiazolecarboxilic acid ester derivative can be synthesized by allowing the compound (S1) to react with a commercially available compound (S2) in an inert alcohol solvent such as ethyl alcohol or in acetic acid at a temperature of from 0°C to boiling point of the solvent.

The compound represented by the formula (A1) can be converted into a compound represented by the formula (A2) such as 2-thiazolemethanol or the like making use of known reduction method (step 1b). The reaction of step 1b can be effected by carrying out the reduction using a reducing agent such as sodium borohydride in an inert alcohol solvent such as ethyl alcohol at a temperature of from -20 to 50°C, preferably from 0°C to room temperature.

The 2-thiazolecarboaldehyde represented by formula (A3) can be synthesized by a known method in which the hydroxyl group of the compound represented by formula (A2) is oxidized into aldehyde (step 1c). For example, the compound of formula (A3) can be synthesized by chromic acid-aided oxidation or

Swern oxidation of the compound of formula (A2) in an inert halogenated hydrocarbon solvent such as m thylene chloride at a temperature of from -90°C to boiling point of the solvent, preferably from -78°C to room temperature. The compound (A3) can also be obtained by treating the compound of formula (A2) with activated manganese dioxide in an inert hydrocarbon solvent such as toluene or an inert ketone solvent such as acetone at a temperature of from 0°C to boiling point of the solvent, preferably from room temperature to boiling point of the solvent.

The compound represented by formula (A4) can be produced by a known reaction in which the compound of formula (A3) is allowed to react with carbon tetrabromide and a phosphorus reagent such as triphenylphosphine in an inert halogenated hydrocarbon solvent such as methylene chloride at a temperature of from -20°C to boiling point of the solvent, preferably from 0°C to room temperature (step 1d).

The compound represented by formula (A5) such as 2-ethynylthiazole or the like can be produced by treating the compound of formula (A4) such as 1,1-dibromo-2-(2-thiazolyl)ethylene with 1.8 to 3 equivalents of an alkyl lithium such as n-butyl lithium in an inert ether solvent such as tetrahydrofuran at a temperature of from -90°C to room temperature, preferably from -78°C to 0°C, and then neutralizing the reaction solution with a dilute mineral acid such as dilute hydrochloric acid or saturated ammonium chloride

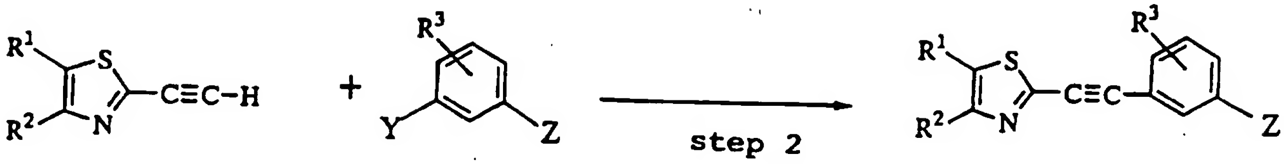
aqueous solution also at a low temperature of for example from -90°C to 30°C, preferably from -78°C to 0°C (step 1).

As an alternative method, the 2-ethynylthiazole or the like compound represented by formula (A5) can be converted directly from the compound of formula (A3) by a known rearrangement reaction. For example, 2-thiazolecarboaldehyde (A3) can be converted into the compound of formula (A5) by treating the former compound with carbanion prepared for example from trimethylsilyldiazomethane and lithium diisopropylamide or the like non-nucleophilic strong base in an inert ether solvent such as tetrahydrofuran and in a stream of an inert gas such as nitrogen gas at a low temperature, preferably at -50°C or lower, and then increasing the temperature to -20°C to boiling point of the solvent, preferably to 0°C to room temperature (step 1f).

Next, a method for the synthesis of a compound represented by the formula (A6) from the compounds represented by formulae (A5) and (S3) is described.

<u>Reaction 2</u>

The compound of formula (A6) can be synthesized by carrying out the following reaction (step 2) of the compound of formula (A5) with the compound of formula (S3).



(A5) (S3) (A6)

(In the above reaction formula, R^1, R^2 and R^3 are as defined in the foregoing, Y represents a halogen atom or a fluoro-alkylsulfonyloxy group and Z represents a nitro group or a group $-CO-R^{10}$, in which R^{10} is a hydroxyl group or an alkoxyl group which may have a substituent.)

In this case, Y in the material compound of formula (S3) represents a halogen atom or a fluoroalkylsulfonyloxy or the like leaving group. For example, trifluoromethanesulfonyl-oxy group may be used as the fluoroalkylsulfonyloxy group. Preferred example of Y is an iodine atom.

When Z is a group $-CO-R^{10}$, R^{10} is preferably an alkoxyl group which may have a substituent, more preferably a methoxy or ethoxy group.

The compound (S3) in this case is selected from 3-iodonitrobenzenes or 3-iodobenzoic acid esters, and these compounds can be obtained commercially or produced by known techniques.

The compound represented by formula (A6) can be synthesized by allowing the compound (S3) to react with the compound represented by formula (A5) in an inert solvent in the

usual way.

Examples of the inert solvent to be used in this reaction include an inert ether solvent such as tetrahydrofuran or 1,2-dimethoxyethane, an organic amine solvent such as triethylamine or diisopropylamine and an inert polar solvent such as N,N-dimethylformamide. Also, the compound of formula (A6) can be obtained by allowing the compound (A5) to react with a monovalent copper halide to form a copper acetylide of compound (A5) and then allowing the product to react with the compound represented by formula (S3). This reaction can be carried out at a temperature of from 0°C to boiling point of the solvent.

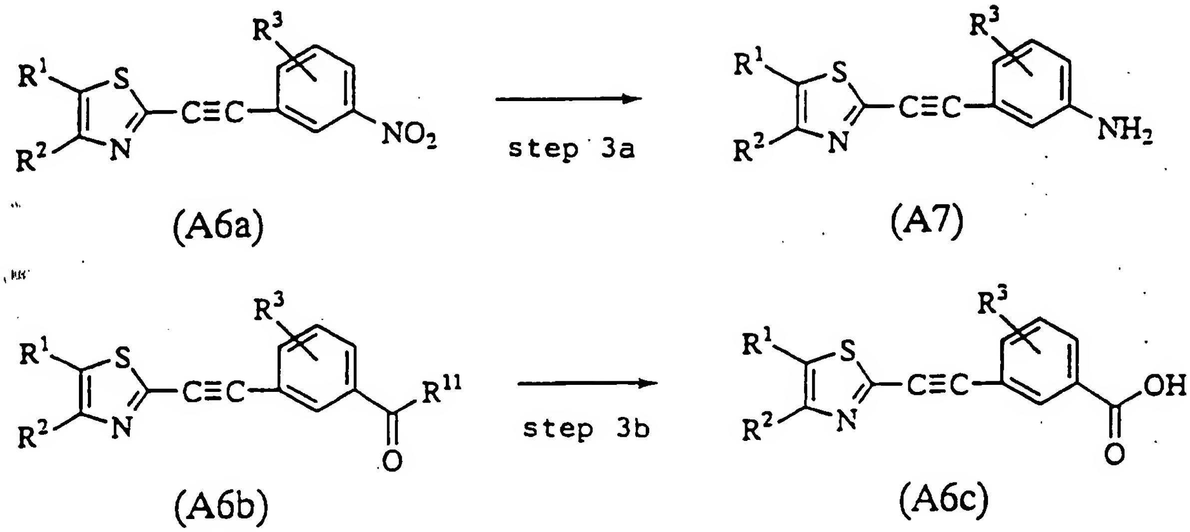
Alternatively, the compound (A6) can be synthesized by carrying out the reaction in the presence or absence of triphenylphosphine and cuprous iodide by adding catalytically effective amount (preferably 0.1 to 10 mol %) of an organic palladium reagent such as palladium[II] acetate, tetrakis-(triphenylphosphine) palladium[0], bis(triphenylphosphine) palladium[II] dichloride or the like.

This reaction can be effected by carrying out a coupling reaction in a stream of an inert gas such as nitrogen, argon or the like at a temperature of from 0°C to boiling point of the solvent (step 2).

<u>Reaction 3</u>

Compounds represented by formulae (A7) and (A6c) can be synthesized from the compound of formula (A6) by the following

steps (st ps 3a and 3b).



(In the above reaction formulae, R^1, R^2 and R^3 are as defined in the foregoing and R^{11} represents an alkoxyl group which may have a substituent.)

A method for the synthesis of the compound represented by formula (A7) is described (reaction step 3a). 3-(2-(2-Thiazolyl)ethynyl)nitrobenzene (A6a), an example of the aforementioned compound (A6) in which Z is a nitro group, can be converted into 3-(2-(2-thiazolyl)ethynyl)aniline (A7) making use of a known reducing agent.

When tin(II) chloride or similar compound is used as the reducing agent, the reaction can be carried out using an inert alcohol solvent such as ethyl alcohol at a temperature of from 0°C to boiling point of the solvent and, when tin, copper or the like metal is used as the reducing agent, the reaction

can be carried out using a diluted mineral acid such as dilute hydrochloric acid or a mixture of dilute hydrochloric acid or the like mineral acid and dioxane or the like inert ether solvent at a temperature of from 0°C to boiling point of the solvent.

After completion of the reaction, the thus obtained acidic solution is adjusted to slightly alkaline range to effect conversion into corresponding compound (A7).

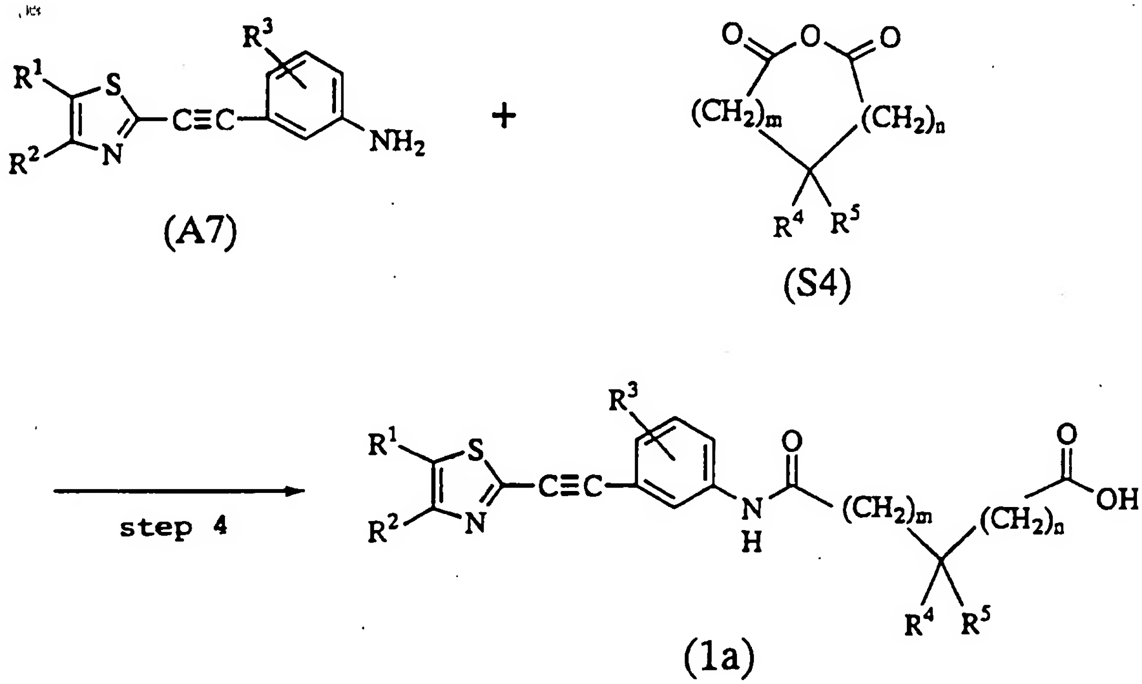
Also, 3-(2-(2-thiazolyl)ethynyl)benzoic acid or the like compound represented by formula (A6c) can be obtained by carrying out hydrolysis of a 3-(2-(2-thiazolyl)ethynyl)benzoic acid ester, an example of compound (A6b) in which Z in the aforementioned formula (A6) is an alkoxycarbonyl group which may have a substituent, under an acidic or alkaline condition.

According to the production process of the above compound, the compound represented by formula (A6b) can be converted into a free carboxylic acid (A6c) by hydrolyzing the starting material in (i) a mineral acid such as hydrochloric acid, (ii) a mineral acid such as hydrochloric acid and an inert ether solvent such as tetrahydrofuran or (iii) a mixture of a mineral acid such as hydrochloric acid and an inert alcohol solvent such as ethyl alcohol, or by hydrolyzing the material in (iv) an aqueous solution of hydroxide of an alkali metal such as sodium hydroxide or of an alkaline earth metal such as barium hydroxide or (v) a mixture of an alkali metal or alkaline earth metal hydroxide and an inert alcohol solvent

such as ethyl alcohol, at a temperature of from -10°C to boiling point of the solvent and, in the case of alkali hydrolysis, acidifying the reaction solution (step 3b).

<u>Reaction 4</u>

Next, a final compound represented by formula (1a) can be synthesized in the following manner (step 4).



(In the above reaction formula, R^1, R^2, R^3, R^4 and R^5 are as defined in the foregoing, n is 0 or 1 and m is an integer of from 1 to 3.)

In the above step 4, the compound of formula (A7) can be converted into a carboxylic acid derivative (1a) by carrying out acylation with a cyclic acid anhydride (S4).

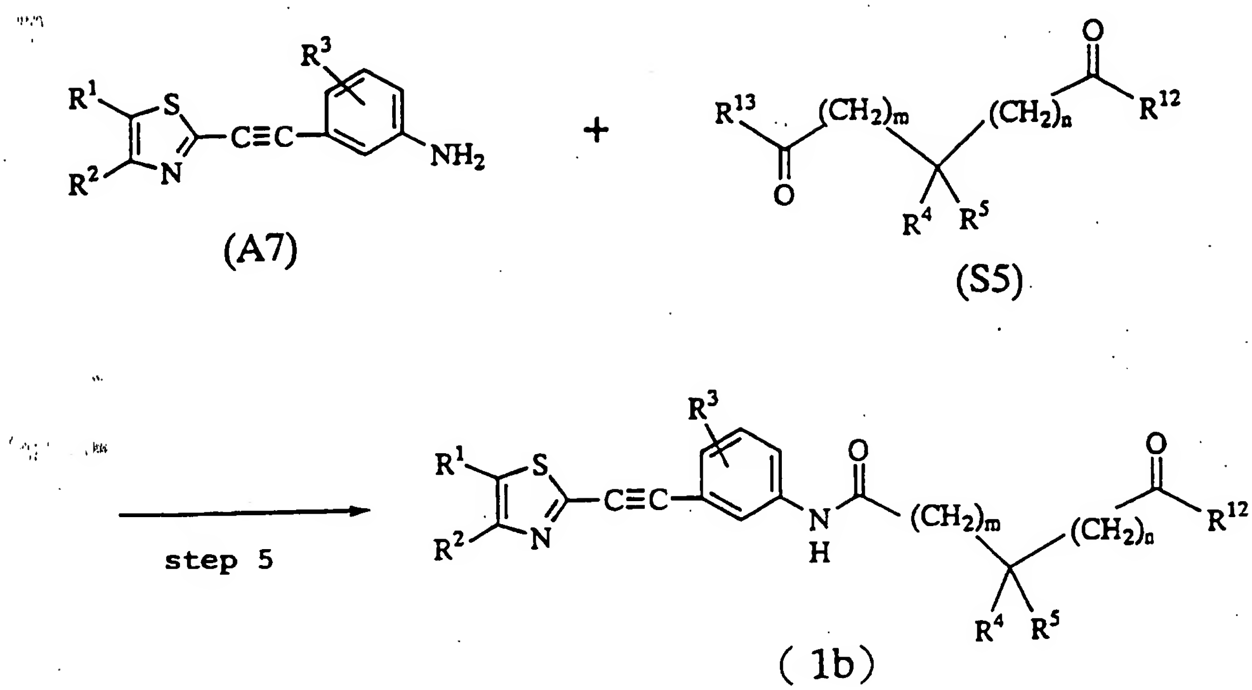
The compound represented by formula (S4) can be obtained commercially or produced making use of known

techniques.

The corresponding final compound (1a) can be obtain d by allowing the compound of formula (A7) to react with the compound (S4) in an inert solvent in the presence of a base at a temperature of from -10°C to boiling point of the solvent and then neutralizing the reaction solution with a mineral acid such as dilute hydrochloric acid. Examples of the inert solvent to be used in this reaction include an inert halogenated hydrocarbon solvent such as methylene chloride, an inert hydrocarbon solvent such as toluene and an inert ether solvent such as tetrahydrofuran, and examples of the base to be used include an inert organic amine such as triethylamine and an inert inorganic base such as sodium acetate.

Reaction 5

Next, a compound represented by formula (1b) can be synthesized from the compound of formula (A7) by a reaction step 5 (step 5).



(In the above reaction formula, R^{12} represents an alkoxyl group which may have a substituent, R^{13} represents a hydroxyl group or a halogen atom and R^1, R^2, R^3, R^4, R^5, m and n are as defined in the foregoing.) In this connection, R^{13} means a leaving group such as a halogen atom or an analog thereof.

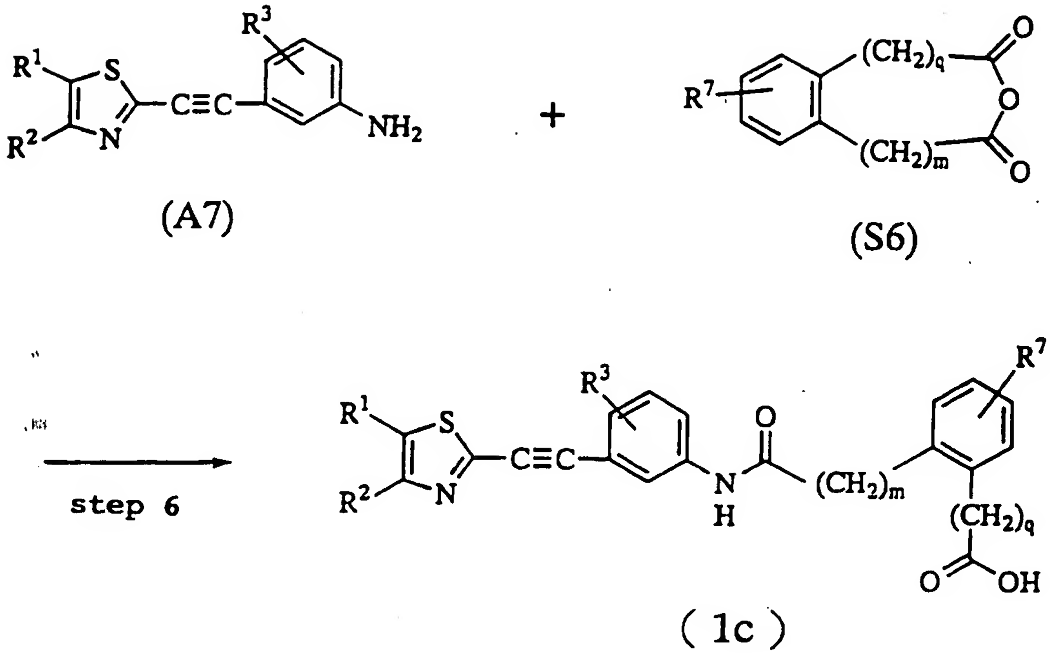
In the step 5, the compound represented by formula (1b) is produced by treating the compound of formula (A7) with an acid chloride represented by the formula (S5) (a case in which R^{13} is a halogen or the like leaving group) in accordance with the following known method. For example, the compound of formula (1b) can be produced by carrying out acylation of the compound (A7) with the compound (S5) in an inert halogenated hydrocarbon solvent such as methylene chloride or an inert ether solvent such as tetrahydrofuran in the presence of an inert organic amine such as triethylamine or pyridine at a

temperature of from -20°C to boiling point of the solvent, preferably from 0°C to room temperature.

As an alternative method, the compound represented by formula (1b) is produced by subjecting the compound of formula (A7) to acylation with a monocarboxylic acid (S5) (a case in which R^{13} is a hydroxyl group). For example, the compound of formula (1b) can be produced by carrying out acylation of the compound (A7) with the compound (S5) using a condensing agent in an inert solvent at a temperature of from -20°C to boiling point of the solvent, preferably from 0°C to room temperature. Examples of the inert solvent useful in this reaction include methylene chloride or the like inert halogenated hydrocarbon solvent, tetrahydrofuran or the like inert ether solvent and N,N-dimethylformamide, and examples of the condensing agent include N,N'-dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole and other similar compounds.

Reaction 6

Next, a compound represented by the formula (1c) can be synthesized by allowing the compound of formula (A7) to react with a compound represented by the formula (S6) (step 6).

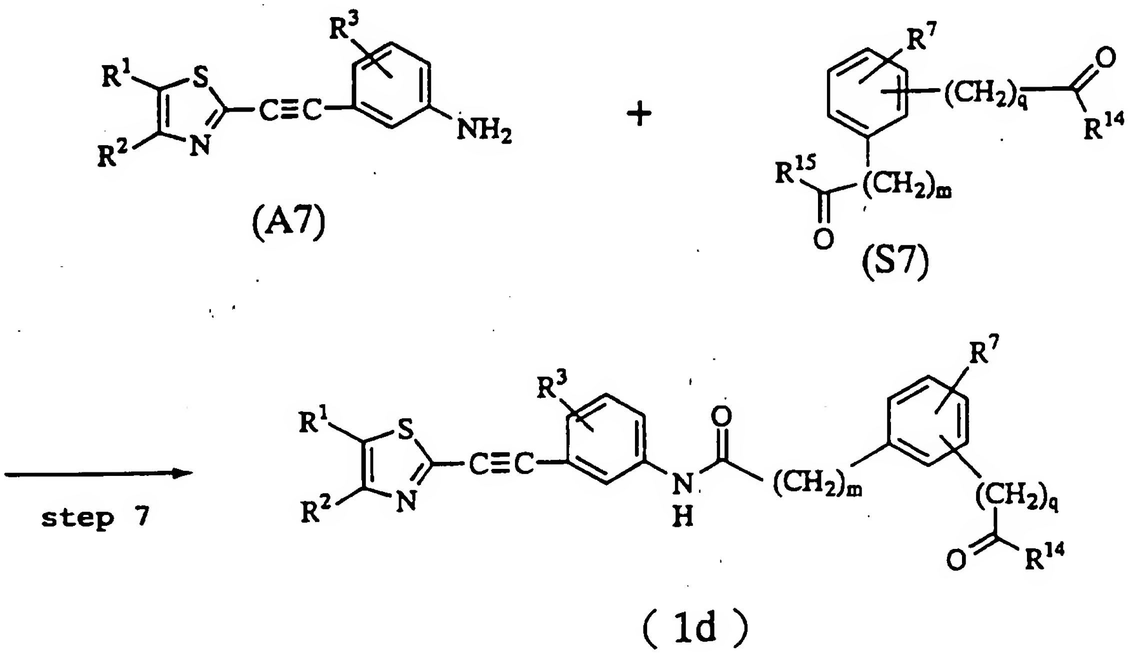


(In the above reaction formula, m is an integer of 0 to 3 when q is 0, or an integer of 1 to 3 when q is 1, and R^1, R^2, R^3 and R^7 are as defined in the foregoing.)

In the step 6, the final compound (1c) can be obtained by allowing the compound of formula (A7) to react with the compound (S6) which can be obtained commercially or produced by a known method, in an inert solvent and in the presence of a base at a temperature of from -10°C to boiling point of the solvent. Examples of the inert solvent useful in this reaction include methylene chloride or the like inert halogenated hydrocarbon solvent, toluene or the like inert hydrocarbon solvent and tetrahydrofuran or the like inert ether solvent, and examples of the base include triethylamine or the like organic base and sodium acetate or the like inorganic base.

Reaction 7

Next, by a step 7, a compound represented by the formula (1d) can be synthesized from the compound of formula (A7) and a compound represented by the formula (S7) (step 7).



(In the above reaction formula, R^{14} represents an alkoxyl group which may have a substituent, R^{15} represents a hydroxyl group or a halogen atom, R^1, R^2, R^3, R^7, m and q are as defined in the foregoing and R^{15} is a leaving group.)

In the step 7, an acid chloride can be exemplified as the compound represented by formula (S7) (a compound in which R^{15} is a halogen atom). The compound of formula (S7) is a known substance or can be synthesized by a known method.

The compound represented by formula (1d) can be synthesized by subjecting the compound of formula (A7) to

acylation together with a compound of the formula (S7), such as an acid chloride(S7), in an inert solvent in the presence of a base at a temperature of from -20°C to boiling point of the solvent, preferably from 0°C to room temperature. Examples of the inert solvent useful in this reaction include an inert halogenated hydrocarbon solvent such as methylene chloride and an inert ether solvent such as tetrahydrofuran, and examples of the useful base include organic bases such as triethylamine and pyridine.

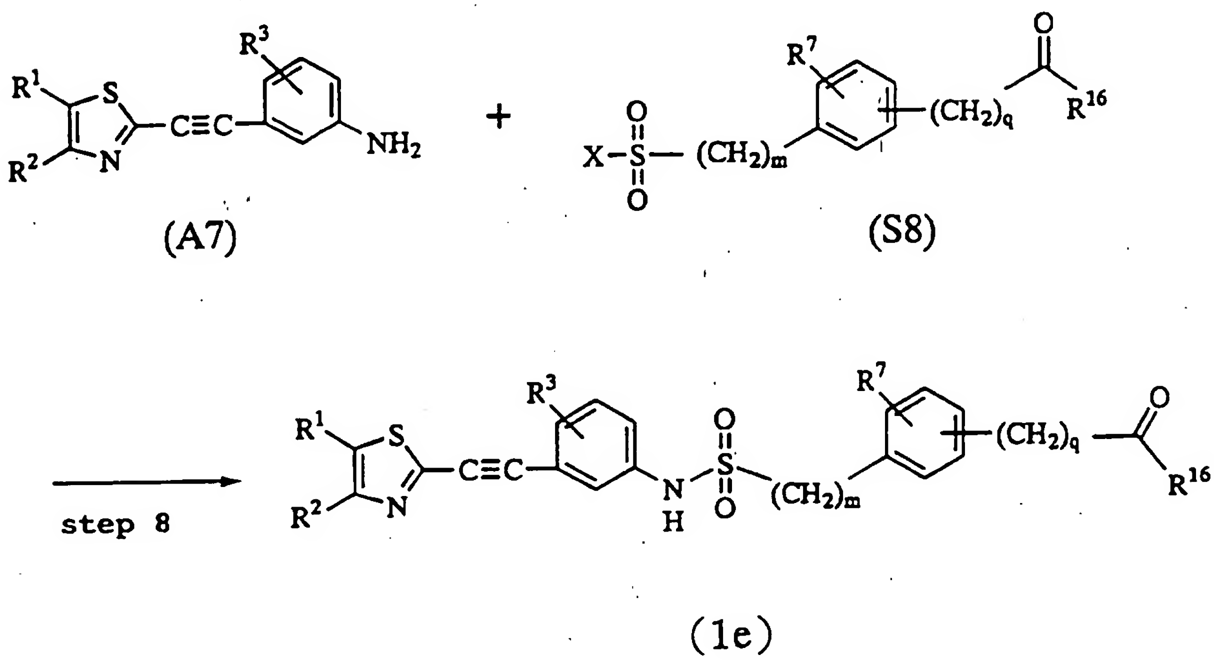
As an alternative method, the compound represented by formula (1d) can be synthesized by allowing the compound of formula (A7) to react with a monocarboxylic acid (S7) (a compound in which R^{15} is a hydroxyl group). The compound (S7) is a known substance or can be synthesized by a known method.

The compound of formula (1d) can be produced by carrying out acylation of the compound (A7) with the compound (S7) using a condensing agent in an inert solvent at a temperature of from -20°C to boiling point of the solvent, preferably from 0°C to room temperature. Examples of the inert solvent useful in this reaction include methylene chloride or the like inert halogenated hydrocarbon solvent, tetrahydrofuran or the like inert ether solvent and N,N-dimethylformamide or the like inert polar solvent, and examples of the condensing agent include N,N'-dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole and other similar compounds.

Reaction 8

Next, a method for the synthesis of a compound represented by formula (1e) is described.

By a step 8, the compound represented by formula (1e) can be synthesized from the compound of formula (A7) and a compound represented by formula (S8) (step 8).



(In the above reaction formula, R^{16} means hydroxyl group or an alkoxyl group which may have a substituent and R^1, R^2, R^3, R^7, m, q and X are as defined in the foregoing.)

In the step 8, the compound represented by formula (1e) can be synthesized by allowing the compound of formula (A7) to react with a compound of the formula (S8).

The compound of formula (S8) can be obtained commercially or produced by a known method, and examples of the

compound of formula (S8) include sulfonyl chlorid s.

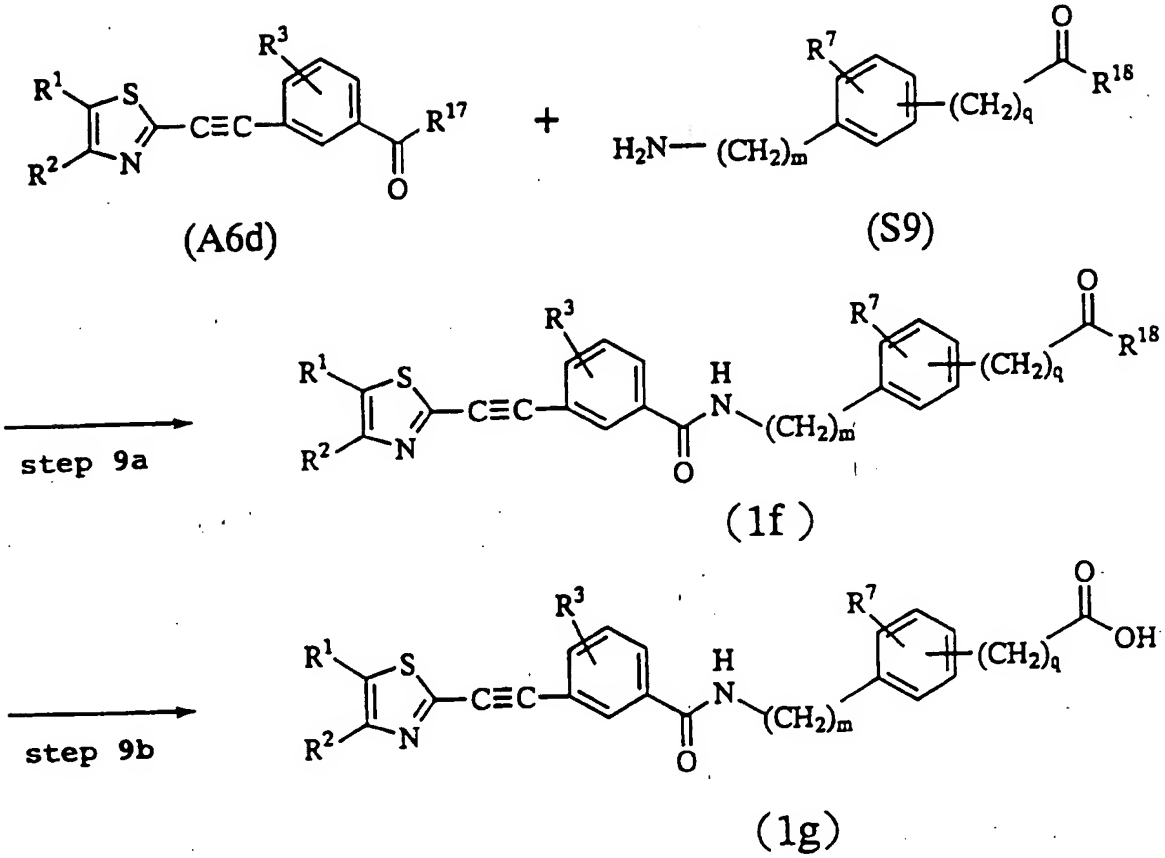
The compound represented by formula (1e) can b produced by allowing the compound of formula (A7) to react with the compound of formula (S8) in an inert solvent in the presence of a base at a temperature of from -10°C to boiling point of the solvent, preferably from 0°C to room temperature.

Examples of the inert solvent useful in this reaction include an inert halogenated hydrocarbon solvent such as methylene chloride, an inert hydrocarbon solvent such as toluene and an inert ether solvent such as tetrahydrofuran, and examples of the useful base include organic bases such as triethylamine and pyridine and inorganic bases such as sodium acetate.

Reaction 9

The following describes synthesis of a compound represented by the formula (1f).

The compound represented by formula (1f) can be obtained by allowing the compound of formula (A6d) to react with a compound of the formula (S9) (step 9a).



(In the above reaction formula, R^{17} represents a hydroxyl group or a leaving group such as a halogen atom or similar substance, R^{18} represents an alkoxyl group which may have a substituent, and R^1, R^2, R^3, R^7, m and q are as defined in the foregoing.)

The compound represented by formula (1f) can be synthesized by allowing the compound of formula (A6d) to react with the compound represented by formula (S9). Also, the compound represented by formula (1g) can be obtained by hydrolyzing the compound of formula (1f).

Methods for the synthesis of the compounds represented

by formulae (1f) and (1g) are describ d.

As shown in step 9a, esters represent d by formula (1f) can be produced by subjecting a benzoic acid derivative represented by the formula (A6d) (an example of (A6c) in which R^{17} is a hydroxyl group) to acylation together with amines of the formula (S9) in an inert solvent in the presence of a condensing agent at a temperature of from -20°C to boiling point of the solvent, preferably from 0°C to room temperature. In this connection, the amines (S9) can be obtained commercially or produced by a known method, examples of the inert solvent useful in this reaction include methylene chloride or the like inert halogenated hydrocarbon solvent, toluene or the like inert hydrocarbon solvent, tetrahydrofuran or the like inert ether solvent and N,N-dimethylformamide, and examples of the condensing agent include N,N'-dicyclohexyl-carbodiimide, N,N'-carbonyldiimidazole and other similar compounds.

As an alternative method, the compound represented by formula (1f) can be obtained by allowing an acid chloride of formula (A6d) (a case in which R^{17} is a halogen atom) to react with a compound of (S9). The acid chloride (A6d) to be used in this reaction can be produced by allowing a benzoic acid derivative (A6c) which can be obtained by the step 3b to react with a chlorination agent in an inert solvent at a temperature of from room temperature to boiling point of the solvent. Examples of the inert solvent useful in this reaction include

toluene or the like inert hydrocarbon solvent and methylene chloride or the like inert halogenated hydrocarbon solvent, and examples of the chlorination agent include thionyl chloride and other similar compounds.

The compound represented by formula (1f) can be synthesized by allowing the compound of formula (A6d) to react with amines (S9) in an inert solvent in the presence of a base at a temperature of from -10°C to boiling point of the solvent, preferably from 0°C to room temperature. The amines represented by formula (S9) can be obtained commercially or produced by a known method. Examples of the inert solvent useful in this reaction include an inert halogenated hydrocarbon solvent such as methylene chloride, an inert hydrocarbon solvent such as toluene and an inert ether solvent such as tetrahydrofuran, and examples of the usable base include organic bases such as triethylamine and pyridine and inorganic bases such as sodium acetate.

In addition, the ester represented by formula (1f) can be converted into a compound represented by the formula (1g) by a known hydrolysis reaction with an acid or an alkali.

The compound having free carboxylic acid represented by formula (1g) can be produced by carrying out hydrolysis of the ester represented by formula (1f) in an acid or an alkali or their mixture with an inert solvent at a temperature of from -10°C to boiling point of the solvent, and, in the case of alkali hydrolysis, further acidifying the reaction solution.

This hydrolysis reaction can be carried out in (i) a mineral acid such as hydrochloric acid, (ii) a mixtur of an inert ether solvent such as tetrahydrofuran with an acid or a mixture of an inert alcohol solvent such as ethyl alcohol with an acid, (iii) an aqueous solution of hydroxide of an alkali metal such as sodium hydroxide or of an alkaline earth metal such as barium hydroxide or (iv) a mixture of an inert alcohol solvent such as ethyl alcohol and an alkali metal or alkaline earth metal hydroxide.

Since these compounds are strong leukotriene antagonists, they are useful in treating various diseases in which leukotriene takes part, such as bronchial asthma, lung anaphylaxis, cystic fibrosis, chronic bronchitis, bronchiectasis, respiratory distress syndrome, pulmonary edema, psoriasis, nephritis, cerebral ischemia-induced brain edema and cerebrovascular spasm and angina pectoris caused by the reduction of coronary blood flow, as well as hepatitis and the like.

An object of the present invention is to provide compounds of the formula (1), physiologically acceptable salts thereof and optical isomers thereof. Its another object is to provide an allergic disease treating agent and a leukotriene antagonist, which contains the compound of formula (1) as active ingredient. The allergic disease treating agent means an agent for use in the treatment or prevention of diseases such as bronchial asthma, lung anaphylaxis, cystic fibrosis,

chronic bronchitis, bronchiectasis, respiratory distr ss syndrome, pulmonary edema and the like.

When the compounds of formula (1), salts thereof and optical isomers thereof have a carboxyl group, they generally form salts with carboxylic acid, all bases which do not exert disadvantageous physiological influences upon the living body are included within the scope of the present invention. In consequence, examples of the suitable salts are any of organic and inorganic salts which include alkali metal salts such as lithium salt, sodium salt, potassium salt and the like, alkaline earth metal salts such as magnesium salt, calcium salt and the like, and ammonium salt, triethylamine salt, N-methylglucamine salt, tris(hydroxymethyl)aminomethane salt and the like. In addition, the free form and carboxyl group salt of these carboxylic acid derivatives may exist as hydrates in some cases.

On the other hand, the ethynylthiazole derivatives whose carboxylic acid moiety is in a ester form are useful as synthetic intermediates of the compounds of the present invention or as prodrugs. For example, alkyl esters, benzyl esters, alkoxyalkyl esters, phenylalkyl esters and phenyl esters are useful as synthetic intermediates, and acetoxymethyl ester, pivaloyloxymethyl ester, choline ester, dimethylaminoethyl ester, 5-indanyl ester and the like are useful as prodrugs.

The compounds of formula (1), salts thereof, optical

isomers thereof or compositions containing th m can b administered by known techniques in the art. In consequenc , each of the compounds of formula (1), salts thereof or optical isomers thereof, alone or together with other pharmaceutical reagent such as an antihistaminic, a mediator release inhibitor, a xanthine derivative, a beta (β) stimulant or an antiasthma steroid such as prednisolone or prednisoline, can be administered orally, parenterally or rectally or by inhalation in the form of aerosols, fine pulverized powders or sprays. In the case of oral administration, these compounds can be administered in the form of tablets or capsules by mixing them with a physiologically acceptable carrier such as talc, starch, lactose or other inert component or in the form of solutions, suspensions, elixirs or aqueous alcoholic solutions by mixing them with sugars or other sweeteners, flavors, coloring agents, thickening agents and other usually used pharmaceutical fillers.

In the case of parenteral administration, they can be administered in the form of solutions or suspensions, such as aqueous or peanut oil solutions or suspensions using fillers and carriers usually used in this administration form. When administered as aerosols, they can be mixed with physiologically acceptable fillers and the like by dissolving them in a suitable physiologically acceptable solvent such as ethyl alcohol or a combination of miscible solvents. In using such an aerosol composition, it is packed in a pressurized

container equipped with an aerosol valve suitable for the release of the pressuriz d composition. Preferably, th aerosol valve is a measuring valve which can release predetermined effective dose of the aerosol composition when functioned.

In the practice of the present invention, dose and administration frequency of the compounds of formula (1), salts thereof and optical isomers thereof to be administered are dependent upon potency and duration of activities of the specified compounds of formula (1), salts thereof and optical isomers thereof, as well as route of administration and weight, age and the like of animals to be treated. Oral dose of the compounds of formula (1), salts thereof and optical isomers thereof to be used in the practice of the present invention is within the range of from about 0.1 mg to 1,000 mg, preferably from about 0.1 mg to about 250 mg, per day, and the daily dose may be divided into 1 to several doses per day.

BEST MODE FOR CARRYING OUT INVENTION

The present invention will now be illustrated in greater detail with reference to Examples, but it should be understood that the present invention is not deemed to be limited thereto

The terms "IR", "NMR" and "MS" used in the examples respectively mean "infrared absorption spectrum", "nuclear magnetic resonance spectrum" and "mass spectrometry". The ratio of solvents described in relation to the chromatographic

separation indicates volume ratio. Unless otherwise noted, "IR" shows results of measurement by KBr tablet method. The solvent shown in parenthesis of "NMR" data indicates measuring solvent, and tetramethylsilane (TMS) is used as the internal standard in all NMR measurement.

Inventive Example 1

Ethyl 4-cyclobutyl-2-thiazolecarboxylate (1):

A 9 g portion of ethyl thiooxamate and 11.96 g of bromomethylcyclobutylketone were heated under reflux for 2 hours in 70 ml of ethanol. After cooling, the reaction solution was concentrated. The resulting residue was mixed with 200 ml of methylene chloride and washed with saturated sodium carbonate and saturated brine in that order. The methylene chloride layer was dried over anhydrous sodium sulfate and then evaporated. The resulting oily residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 8:1) to obtain 13.7 g of the title compound (1) as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.43 (3H, t), 1.88 - 2.44 (6H, m), 3.78 (1H, quint), 4.48 (2H, q), 7.23 (1H, s).

Inventive Example 2

Ethyl 4-isopropyl-2-thiazolecarboxylate (2):

A 13.8 g portion of ethyl thiooxamate and 19.0 g of bromomethylisopropylketone were heated under reflux for 2 hours in 150 ml of ethanol. After cooling, the reaction solution was

concentrated. The resulting residue was mixed with 200 ml of methylene chloride, and washed with saturat d sodium carbonate and saturated brine in that order. The methylene chloride layer was dried over anhydrous sodium sulfate and then evaporated. The resulting oily residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 8:1) to obtain 17.9 g of the title compound (2) as pale brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.34 (6H, d), 1.44 (3H, t), 3.25 (1H, m), 4.48 (2H, q), 7.20 (1H, s).

Inventive Example 3

4-Cyclobutyl-2-thiazolemethanol (3):

A 13.7 g portion of the compound (1) was dissolved in 60 ml of ethanol, and 2.45 g of sodium borohydride was gradually added to the solution which was cooled in an ice bath. The reaction solution was stirred at room temperature for 8 hours. With cooling in an ice bath, the reaction solution was mixed with water to effect decomposition of excess sodium borohydride and then extracted with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and then evaporated to obtain 8.39 g of the title compound (3) as pale brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.85 - 2.43 (6H, m), 3.63 (1H, quint), 3.77 (1H, br), 4.91 (2H, d), 6.86 (1H, s).

Inventive Example 4

4-Isopropyl-2-thiazolemethanol (4):

A 17.9 g portion of the compound (2) was dissolved in 200 ml of ethanol, and 5.05 g of sodium borohydride was gradually added to the solution which was cooled in an ice bath. The reaction solution was stirred at room temperature for 8 hours. With cooling in an ice bath, the reaction solution was mixed with water to effect decomposition of excess sodium borohydride and then extracted with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and then evaporated to obtain 10.6 g of the title compound (4) as pale yellow powder.

Melting point: 78 - 79°C.

IR (KBr) ν max (cm^{-1}): 3132.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.28 (6H, d), 3.06 (1H, m), 4.26 (1H, br), 4.91 (2H, d), 6.84 (1H, s).

MS (EI) m/z: 157 (M^+).

Inventive Example 5

4-Cyclobutyl-2-thiazolecarbaldehyde (5):

a) A 43.2 g portion of oxalyl dichloride was dissolved in 350 ml of methylene chloride to which, with stirring at -70°C, was subsequently added dropwise 53.1 g of dimethyl sulfoxide (DMSO). After completion of the addition, the stirring was continued for 0.5 hour at the same temperature. To this solution was added dropwise 100 ml of methylene

chloride solution containing 28.8 g of the compound (3) at the same temperature. After completion of the addition, the stirring was continued for 1 hour and then 103 g of triethylamine was added. The reaction solution was warmed up to room temperature, mixed with 100 ml of water and then extracted twice with 500 ml of ether. The extract was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was evaporated under a reduced pressure and the resulting residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 8:1) to obtain 19.9 g of the title compound (5) as pale yellow oil.

b) A 1.18 g portion of the compound (3) and 1.21 g of activated manganese dioxide were heated under reflux for 4 hours in 50 ml of toluene. After cooling, insoluble matter was filtered off using celite under a reduced pressure. The filtrate was evaporated under a reduced pressure and the resulting residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 8:1) to obtain 800 mg of the title compound (5) as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.92 - 2.48 (6H, m), 3.76 (1H, quint), 7.35 (1H, s), 9.99 (1H, s).

Inventive Example 6

4-Isopropyl-2-thiazolecarbaldehyde (6):

A 10.0 g portion of the compound (4) and 16.7 g of activated manganese dioxide were heated under reflux for 2

hours in 150 ml of toluene. After cooling, insoluble matter was filtered off using c lite under a r duc d pressure. Th filtrate was evaporated under a reduced pressure and the resulting residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 8:1) to obtain 7.94 g of the title compound (6) as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.37 (6H, d), 3.22 (1H, m), 7.35 (1H, s), 9.98 (1H, s).

Inventive Example 7

1,1-Dibromo-2-(4-cyclobutyl-2-thiazolyl)ethylene (7):

A 3.97 g portion of carbon tetrabromide was dissolved in 50 ml of methylene chloride to which was subsequently added 6.27 g of triphenylphosphine at -10°C. To this solution was added dropwise 5 ml of methylene chloride solution containing 1 g of the compound (5) at the same temperature. After completion of the addition, the reaction solution was warmed up to room temperature. The reaction solution was neutralized by adding aqueous solution of saturated sodium hydrogencarbonate and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate, the solvent was evaporated under a reduced pressure and then the resulting oily residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 4:1) to obtain 1.9 g of the title compound (7) as pale brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.89 - 2.41 (6H, m), 3.68 (1H, quint), 7.02 (1H, s),

7.95 (1H, s).

Inventive Example 8

4-Cyclobutyl-2-ethynylthiazole (8):

a) A 1.48 g portion of the compound (7) was dissolved in 20 ml of tetrahydrofuran to which, with stirring at -70°C in a stream of nitrogen, was subsequently added dropwise 6.1 ml of n-butyl lithium (1.5 M solution in n-hexane). After completion of the dropwise addition, the reaction solution was stirred for additional 1 hour at the same temperature. To the reaction solution was added 50 ml of saturated ammonium chloride aqueous solution and then warmed up to room temperature. The reaction solution was extracted twice with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous magnesium sulfate. The solvent was evaporated under a reduced pressure and the resulting oily residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 8:1) to obtain 546 mg of the title compound (8) as pale brown oil.

b) In a stream of nitrogen and at a temperature of -50 to -78°C, 59 ml of n-butyl lithium (1.7 M solution in n-hexane) was added dropwise to 100 ml of tetrahydrofuran solution containing 10.1 g of diisopropylamine. After 30 minutes of stirring at 0°C and subsequent cooling to -78°C, 50 ml of trimethylsilyldiazomethane (2.0 M solution in n-hexane) was added dropwise to the resulting solution while keeping the solution temperature at -50°C or below. After completion of

the addition, the reaction solution was stirred for 30 minutes at -78°C. To this solution was added dropwise 100 ml of tetrahydrofuran solution containing 15.8 g of 4-cyclobutyl-2-thiazolecarboaldehyde (5) while keeping the solution temperature at -50°C or below. The reaction solution was stirred at -78°C for 1 hour, at 0°C for 1 hour and then at room temperature for 1 hour. The reaction solution was poured into 300 ml of ice and aqueous solution of saturated ammonium chloride and extracted with ethyl acetate. The extract was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was evaporated under a reduced pressure and the resulting oily residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 8:1) to obtain 11.1 g of the title compound (8) as pale brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.88 - 2.38 (6H, m), 3.44 (1H, s), 3.67 (1H, quint), 6.93 (1H, s).

Inventive Example 9

4-Isopropyl-2-ethynylthiazole (9):

In a stream of nitrogen and at a temperature of from -50 to -78°C, 33 ml of n-butyl lithium (1.71 M solution in n-hexane) was added dropwise to 50 ml of tetrahydrofuran solution containing 5.67 g of diisopropylamine. After 30 minutes of stirring at 0°C and subsequent cooling to -78°C, 28 ml of trimethylsilyldiazomethane (2.0 M solution in n-hexane) was

added dropwise to the resulting solution while keeping the solution temperature at -50°C or below. After completion of the dropwise addition, the reaction solution was stirred for 30 minutes at -78°C. To this solution was added dropwise 20 ml of tetrahydrofuran solution containing 7.90 g of 4-isopropyl-2-thiazolecarbaldehyde (6) while keeping the solution temperature at -50°C or below. The reaction solution was stirred at -78°C for 1 hour, at 0°C for 1 hour and then at room temperature for 1 hour. The reaction solution was poured into 300 ml of ice and aqueous solution of saturated ammonium chloride and extracted with ethyl acetate. The extract was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was evaporated under a reduced pressure and the resulting oily residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 8:1) to obtain 6.36 g of the title compound (9) as pale brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.32 (6H, d), 3.12 (1H, m), 3.44 (1H, s), 6.92 (1H, s).

Inventive Example 10

4-Cyclobutyl-2-(2-(3-nitrophenyl)ethynyl)thiazole (10):

A 519 mg portion of 3-iodonitrobenzene, 40 mg of cuprous iodide and 120 mg of tetrakis(triphenylphosphine) palladium[0] were stirred for 1 hour in 3 ml of diisopropylamine in a stream of nitrogen. To the reaction solution was added dropwise 2 ml of diisopropylamine solution containing 340 mg of the compound (8) at room temperature. The reaction

solution was further stirred at room temperature for 1 hour. The reaction solution was evaporated under a reduced pr ssur and the resulting oily residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 8:1) to obtain 502 mg of the title compound (10) as pale yellow fine needles.

Melting point: 107 - 109°C.

IR (KBr) ν max (cm^{-1}): 1528.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.90 - 2.44 (6H, m), 3.71 (1H, quint), 7.02 (1H, s), 7.57 (1H, t), 7.89 (1H, t), 8.24 (1H, ddd), 8.44 (1H, t).

MS (FAB) m/z: 285 (M^+ + 1).

Inventive Example 11

4-Isopropyl-2-(2-(3-nitrophenyl)ethynyl)thiazole (11):

A 16.6 g portion of 3-iodonitrobenzene, 1.3 g of cuprous iodide and 3.80 g of tetrakis(triphenylphosphine) palladium[0] were stirred for 1 hour at room temperature in 100 ml of diisopropylamine in a stream of nitrogen. To the reaction solution was added dropwise 50 ml of diisopropylamine solution containing 10 g of the compound (9) at room temperature. After completion of the addition, the reaction solution was stirred at room temperature for further 1 hour. The reaction solution was evaporated under a reduced pressure and the resulting oily residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 8:1) to

obtain 12.8 g of the title compound (11) as needles.

Elemental analysis data:

calcd. (%) for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29.

found (%): C, 61.49; H, 4.47; N, 10.13.

Melting point: 64°C.

IR (KBr) ν max (cm^{-1}): 1534, 1352.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.36 (6H, d), 3.17 (1H, m), 7.02 (1H, s), 7.58 (1H, t), 7.89 (1H, dt), 8.25 (1H, dd), 8.45 (1H, t).

MS (FAB) m/z: 285 (M^+ + 1).

Inventive Example 12

3-(2-(4-Cyclobutyl-2-thiazolyl)ethynyl)aniline (12):

A 500 mg portion of the compound (10) and 1.43 g of tin[II] chloride (dihydrate) were heated under reflux for 2 hours in 10 ml of ethanol with stirring. After cooling, the solvent was evaporated. The resulting oily residue, cooled in an ice bath, was alkalified by adding aqueous solution of 4 N sodium hydroxide and then extracted twice with methylene chloride. The methylene chloride layers were combined, washed with saturated brine and then dried over anhydrous magnesium sulfate. The solvent was evaporated under a reduced pressure and the resulting oily residue was purified by a silica-gel column chromatography (eluent: chloroform:ethyl alcohol = 20:1) to obtain 410 mg of the title compound (12) as pale brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.88 - 2.40 (6H, m), 3.69 (1H, quint), 6.71 (1H, dd),

6.89 (1H, s), 6.93 (1H, s), 7.14 (1H, t).

Inventive Example 13

3-(2-(4-Isopropyl-2-thiazolyl)ethynyl)aniline (13):

A 12.3 g portion of the compound (11) and 31 g of tin[II] chloride (dihydrate) were heated under reflux for 2 hours in 70 ml of ethanol with stirring. After cooling, the solvent was evaporated. The resulting oily residue was cooled in an ice bath, alkalified by adding aqueous solution of 4 N sodium hydroxide and then extracted twice with methylene chloride. The methylene chloride layers were combined, washed with saturated brine and then dried over anhydrous magnesium sulfate. The solvent was evaporated under a reduced pressure and the resulting oily residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 4:1) to obtain 10.0 g of the title compound (13) as pale brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.34 (6H, d), 3.14 (1H, m), 6.70 (1H, dd), 6.89 (1H, s), 6.92 (1H, s), 7.14 (1H, t).

Inventive Example 14

Ethyl 3-(2-(4-cyclobutyl-2-thiazolyl)ethynyl)benzoate (14):

A 8.45 g portion of ethyl 3-iodobenzoate, 1.77 g of tetrakis(triphenylphosphine) palladium[0] and 650 mg of cuprous iodide were stirred for 1 hour at room temperature in 100 ml of diisopropylamine in a stream of nitrogen. To the reaction solution was added dropwise 10 ml of diisopropylamine solution containing 5 g of the compound (8), followed by 2 hours of

stirring at room temperature. The reaction solution was evaporated under a reduced pressure and the resulting oily residue was purified by a silica-gel column chromatography (eluent: n-hexane:ethyl acetate = 8:1) to obtain 9.27 g of the title compound (14) as pale brown oil.

IR (KBr) ν max (cm^{-1}): 2220.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.41 (3H, t), 1.91 - 2.42 (6H, m), 3.70 (1H, quint), 4.40 (2H, q), 6.97 (1H, s), 7.46 (1H, t), 7.75 (1H, dt), 8.06 (1H, dt), 8.28 (1H, t).

MS (FAB) m/z: 312 (M^+ + 1).

Inventive Example 15

3-(2-(4-Cyclobutyl-2-thiazolyl)ethynyl)benzoic acid (15):

A 9.28 g portion of the compound (14) was dissolved in 200 ml of tetrahydrofuran, mixed with 240 ml of aqueous solution of 0.25 N sodium hydroxide and then stirred at room temperature for 3 hours. The reaction solution was poured into 50 ml of 1 N hydrochloric acid which was stirred and cooled in an ice bath. The precipitated crystals were collected, washed with water and then air-dried. The thus obtained crude crystals were recrystallized from chloroform-n-hexane to obtain 6.85 g of the title compound (15) as pale yellow fine needles.

Elemental analysis data:

calcd. (%) for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94.

found (%): C, 67.38; H, 4.63; N, 4.94.

Melting point: 139 - 140°C.

IR (KBr) ν max (cm^{-1}): 2220.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:

1.90 - 2.45 (6H, m), 3.76 (1H, quint), 6.97 (1H, s), 7.50 (1H, t), 7.80 (1H, dt), 8.14 (1H, dt), 8.38 (1H, t).

MS (FAB) m/z: 284 (M^+ + 1).

<u>Inventive Example 16</u>

4-(3-(2-(4-Cyclobutyl-2-thiazolyl)ethynyl)phenylamino)-2,2-diethyl-4-oxobutyric acid (16):

A 274 mg portion of 2,2-diethylsuccinic acid and 10 ml of acetyl chloride were heated under reflux for 3 hours with stirring. After cooling, the reaction solution was evaporated to dryness under a reduced pressure. The resulting residue was dissolved in 10 ml of 1,2-dimethoxyethane and mixed with 200 mg of the compound (12) and 322 mg of sodium acetate, and then the mixture was heated under reflux for 2 hours with stirring. After cooling, the reaction solution was concentrated under a reduced pressure. The resulting residue was mixed with 100 ml of water and heated under reflux for 30 minutes. After cooling, the thus obtained crystals were collected by filtration, washed with water and then air-dried. The thus obtained crude crystals were recrystallized from acetonitrile to obtain 260 mg of the title compound (16) as pale yellow fine needles.

Elemental analysis data:

calcd. (%) for $C_{23}H_{26}N_2O_3S$: C, 67.29; H, 6.38; N, 6.82.

found (%): C, 67.04; H, 6.39; N, 6.75.

Melting point: 158 - 160°C.

IR (KBr) ν max (cm^{-1}): 2216.

^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:

0.81 (6H, t), 1.65 (4H, m), 1.86 - 2.30 (6H, m), 2.60 (2H, s), 3.66 (1H, quint), 7.30 (1H, d), 7.39 (1H, t), 7.52 (1H, s), 7.56 (1H, d), 7.95 (1H, s), 10.16 (1H, s), 12.17 (1H, br).

Inventive Example 17

4-(3-(2-(4-Isopropyl-2-thiazolyl)ethynyl)phenylamino)-2,2-diethyl-4-oxobutyric acid (17):

A 548 mg portion of 2,2-diethylsuccinic acid and 20 ml of acetyl chloride were heated under reflux for 3 hours with stirring. After cooling, the reaction solution was evaporated to dryness under a reduced pressure. The resulting residue was dissolved in 20 ml of 1,2-dimethoxyethane and mixed with 400 mg of the compound (13) and 644 mg of sodium acetate, and then the mixture was heated under reflux for 2 hours with stirring. After cooling, the reaction solution was concentrated under a reduced pressure. The resulting residue was mixed with 100 ml of water and heated under reflux for 30 minutes. After cooling, the thus obtained crystals were collected by filtration, washed with water and then air-dried. The thus obtained crude crystals were recrystallized from acetonitrile

to obtain 180 mg of the title compound (17) as pale yellow fin needles.

Elemental analysis data:

calcd. (%) for $C_{22}H_{26}N_2O_3S \cdot 1/4H_2O$: C, 67.29; H, 6.38; N, 6.82.

found (%): C, 67.04; H, 6.39; N, 6.75.

Melting point: 154 - 155°C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:

0.81 (6H, t), 1.26 (6H, d), 1.66 (4H, m), 2.60 (2H, s), 3.66 (1H, m), 7.30 (1H, d), 7.39 (1H, t), 7.48 (1H, s), 7.56 (1H, d), 7.94 (1H, s), 10.10 (1H, s), 12.16 (1H, br).

Inventive Example 18

2-(2-(3-(2-(4-Cyclobutyl-2-thiazolyl)ethynyl)phenylamino)-2-oxoethyl)benzoic acid (18):

With stirring, 200 mg of the compound (12) and 127 mg of homophthalic anhydride were heated under reflux for 10 minutes in 10 ml of toluene. After cooling, the thus obtained crystals were collected by filtration, washed with ether and then air-dried. The obtained crude crystals were recrystallized from ethyl alcohol to obtain 254 mg of the title compound (18) as pale yellow fine needles.

Elemental analysis data:

calcd. (%) for $C_{24}H_{20}N_2O_3S$: C, 69.21; H, 4.84; N, 6.73.

found (%): C, 68.88; H, 4.86; N, 6.68.

Melting point: 201 - 202°C.

IR (KBr) ν max (cm^{-1}): 2216.

^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:

1.83 - 2.32 (6H, m), 3.66 (1H, quint), 4.12 (2H, s), 7.30 (1H, d), 7.37 - 7.55 (5H, m), 7.60 (1H, d), 7.90 (1H, d), 7.94 (1H, s), 10.27 (1H, s), 12.84 (1H, s).

Inventive Example 19

2-(2-(3-(2-(4-Isopropyl-2-thiazolyl)ethynyl)phenylamino)-2-oxoethyl)benzoic acid (19):

With stirring, 470 mg of the compound (13) and 349 mg of homophthalic anhydride were heated under reflux for 30 minutes in 15 ml of toluene. After cooling, the obtained crystals were collected by filtration, washed with ether and then air-dried. The obtained crude crystals were recrystallized from ethyl alcohol to obtain 653 mg of the title compound (19) as pale yellow fine needles.

Elemental analysis data:

calcd. (%) for $C_{23}H_{20}N_2O_3S \cdot 1/4H_2O$: C, 69.21; H, 4.84; N, 6.73.

found (%): C, 68.88; H, 4.86; N, 6.68.

Melting point: 203 - 205°C.

IR (KBr) ν max (cm^{-1}): 2216.

^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:

1.26 (6H, d), 3.07 (1H, m), 4.12 (2H, s), 7.30 (1H, d), 7.33 - 7.43 (3H, m), 7.48 (1H, s), 7.53 (1H, t), 7.60 (1H, d), 7.90 (1H, d), 7.94 (1H, s), 10.28 (1H, s), 12.85 (1H, s).

MS (FAB) m/z: 405 (M^+ + 1).

Inventive Example 20

2-((3-(2-(4-Cyclobutyl-2-thiazolyl)ethynyl)phenylamino)-carbonyl)benzoic acid (20):

With stirring, 305 mg of the compound (12) and 148 mg of phthalic anhydride were heated under reflux for 5 hours in 10 ml of toluene. After cooling, the reaction solution was mixed with 20 ml of n-hexane, and the thus precipitated crystals were collected by filtration. The filtrate was concentrated, the resulting residue was dissolved in 30 ml of methanol, and the solution was mixed with 138 mg of potassium carbonate and stirred for 3 hours at room temperature. The reaction solution was concentrated, mixed with 1 N hydrochloric acid and the thus precipitated crystals were collected by filtration. They were combined with the firstly obtained crystals and recrystallized from chloroform to obtain 201 mg of the title compound (20) as pale yellow fine needles.

Melting point: 173 - 175°C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:

1.83 - 2.33 (6H, m), 3.62 - 3.71 (1H, m), 7.36 (1H, d), 7.44 (1H, t), 7.53 (1H, s), 7.56 - 7.62 (2H, m), 7.66 - 7.71 (2H, m), 7.91 (1H, d), 8.04 (1H, s), 10.55 (1H, s), 13.11 (1H, brs).

Inventive Example 21

Methyl 2-(((3-(2-(4-cyclobutyl-2-thiazolyl)ethynyl)phenyl)-carbonyl)amino)benzoic acid (21):

A 142 mg portion of the compound (15) and 76 mg of methyl 2-aminobenzoate were dissolved in 3 ml of N,N-dimethyl-formamide to which were subsequently added 61 mg of 4-dimethylaminopyridine and 153 mg of 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide hydrochloride, followed by 15 hours of stirring at room temperature. The reaction solution was poured into 100 ml of 1 N hydrochloric acid. The precipitated crystals were collected, washed with water and then air-dried. The thus obtained crystals were dissolved in chloroform, and the solution was dried over magnesium sulfate and then evaporated under a reduced pressure. The resulting residue was purified by a silica-gel column chromatography (eluent: chloroform) to obtain 75 mg of the title compound (21) as fine needles.

Melting point: 168 - 170°C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:

1.91 - 2.40 (6H, m), 3.66 - 3.75 (1H, m), 3.98 (3H, s), 6.98 (1H, s), 7.13 - 7.17 (1H, m), 7.54 (1H, t), 7.60 - 7.64 (1H, m), 7.77 (1H, d), 8.05 (1H, d), 8.09 - 8.11 (1H, m), 8.25 (1H, s), 8.89 - 8.92 (1H, m), 12.08 (1H, s).

Inventive Example 22

2-(((3-(2-(4-Cyclobutyl-2-thiazolyl)ethynyl)phenyl)carbonyl)-amino)benzoic acid (22):

A 62 mg portion of the compound (21) was dissolved in 2 ml of tetrahydrofuran, the solution was mixed with 2 ml of aqueous solution of 0.25 N sodium hydroxide and then the mixture was stirred for 2 hours at room temperature. The reaction solution was diluted with 50 ml of water to which was subsequently added 1 ml of 1 N hydrochloric acid. The precipitated crystals were collected by filtration, washed with water and then air-dried. The obtained crude crystals were recrystallized from chloroform-n-hexane to obtain 47 mg of the title compound (22) as fine needles.

Melting point: 220 - 222°C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:

1.86 - 2.34 (6H, m), 3.64 - 3.72 (1H, m), 7.24 (1H, t), 7.56 (1H, s), 7.71 - 7.66 (1H, m), 7.71 (1H, t), 7.93 (1H, d), 8.06 (1H, d), 8.07 (1H, d), 8.18 (1H, s), 8.65 (1H, d), 12.22 (1H, s), 13.85 (1H, brs).

Inventive Example 23

4-((3-(2-(4-Cyclobutyl-2-thiazolyl)ethynyl)phenylamino)-sulfonyl)benzoic acid (23):

With stirring at room temperature, 254 mg of 4-(chlorosulfonyl)benzoic acid was added to 10 ml of methylene chloride containing 293 mg of the compound (12) and 1 ml of pyridine, and the mixture was stirred for 1 hour. The reaction

solution was diluted with 250 ml of ethyl acetate and then washed with 1 N hydrochloric acid and saturated brine in that order. The ethyl acetate layer was dried over anhydrous magnesium sulfate and then evaporated under a reduced pressure. The obtained crude crystals were recrystallized from chloroform-n-hexane to obtain 219 mg of the title compound (23) as pale yellow fine needles.

Elemental analysis data:

calcd. (%) for $C_{22}H_{18}N_2O_4S_2 \cdot H_2O$: C, 58.02; H, 4.13; N, 5.86.

found (%): C, 57.88; H, 4.42; N, 6.14.

Melting point: 213 - 216°C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm:

1.83 - 2.33 (6H, m), 3.64 (1H, quint), 7.21 - 7.24 (1H, m), 7.31 - 7.40 (3H, m), 7.54 (1H, s), 7.90 (2H, d), 8.10 (2H, d), 10.76 (1H, s).

Formulation Example 1

(Production of tablets)

A 1,000 mg portion of thoroughly pulverized compound (16) was mixed thoroughly with 5,900 mg of lactose, 2,000 mg of micro-crystalline cellulose (MCC), 1,000 mg of low-substituted hydroxypropyl cellulose (LHPC) and 100 mg of magnesium stearate, and the mixture was made into tablets by a direct tabletting method, each tablet weighing 100 mg and containing 10 mg of the aforementioned compound. These uncoated tablets were subjected to sugar coating or film coating to produce

sugar coated tablets or film coated tablets.

Formulation Example 2

(Production of tablets)

A 1,000 mg portion of thoroughly pulverized compound (18) was mixed thoroughly with 5,900 mg of lactose, 2,000 mg of micro-crystalline cellulose (MCC), 1,000 mg of low-substituted hydroxypropyl cellulose (LHPC) and 100 mg of magnesium stearate, and the mixture was made into tablets by a direct tabletting method, each tablet weighing 100 mg and containing 10 mg of the aforementioned compound. These uncoated tablets were subjected to sugar coating or film coating to produce sugar coated tablets or film coated tablets.

Formulation Example 3

(Production of capsules)

A 1,000 mg portion of thoroughly pulverized compound (16) was mixed thoroughly with 3,000 mg of corn starch, 6,900 mg of lactose, 1,000 mg of micro-crystalline cellulose (MCC) and 100 mg of magnesium stearate, and the mixture was filled into capsules, each capsule weighing 120 mg and containing 10 mg of the aforementioned compound.

Formulation Example 4

(Production of capsules)

A 1,000 mg portion of thoroughly pulverized compound (18) was mixed thoroughly with 3,000 mg of corn starch, 6,900 mg of lactose, 1,000 mg of micro-crystalline cellulose (MCC) and 100 mg of magnesium stearate, and the mixture was filled

into capsules, each capsule weighing 120 mg and containing 10 mg of the aforementioned compound.

Formulation Example 5

(Production of inhalations)

A 50 mg portion of sorbitan monooleate was put into a 5 ml aluminum container for aerosol and suspended in 1 ml of Freon-11. A 50 mg portion of thoroughly pulverized and dried compound (16) was added thereto and dispersed by ultrasonic energy. A 100 μℓ metered dose valve was attached to the container, and 4 ml of Freon-12 was packed therein through the valve under pressure. A metered dose inhaler (MDI) was produced in which one spray of 100 μl contains 1 mg of the aforementioned compound.

Formulation Example 6

(Production of inhalations)

A 50 mg portion of sorbitan monooleate was put into a 5 ml aluminum container for aerosol and suspended in 1 ml of Freon-11. A 50 mg portion of thoroughly pulverized and dried compound (18) was added thereto and dispersed by ultrasonic energy. A 100 μℓ metered dose valve was attached to the container, and 4 ml of Freon-12 was packed therein through the valve under pressure. A metered dose inhaler (MDI) was produced in which one spray of 100 μl contains 1 mg of the aforementioned compound.

Since the compounds of formula (1), salts thereof and optical isomers thereof are active as a tracheostenosis

inhibitor, they are useful for example as a bronchopulmonary drug for the alleviation of asthma and allergic reactions. Useful activities of the compound of formula (1) of the present invention can be exemplified as follows.

Test Example 1

(LTD_4 antagonism test using guinea pig isolated ileum)

The antagonism was measured by the Magnus method using the ileum of a male Hartley guinea pig.

A guinea pig was sacrificed by bloodletting and the ileum was isolated therefrom. The ileum was cut in a length of 1 to 1.5 cm and further incised in its longitudinal muscle direction to prepare a ileum preparation. This preparation was placed in a Magnus tube filled with 10 ml of Tyrode solution (35°C, 95% oxygen-5% carbon dioxide mixed gas bubbling) and then 1 g was loaded. After 3 to 4 times of contraction with histamine (10^{-4} M), effect of test compounds on the LTD_4-induced contraction was examined. Contraction of the ileum was recorded on a recorder (manufactured by Rika Denki: R-64VS) via an isotonic transducer (manufactured by Nihon Kohden: TD-112S). Each test compound was dissolved in dimethyl sulfoxide (DMSO) and added to the Magnus tube 5 minutes before the addition of LTD_4 (final concentration: 10^{-8} M). The percentage inhibition was calculated by comparing the response of the ileum treated with solvent and the response of the ileum treated with test compound, and 50% inhibition dose (ID_{50}) was calculated by linear regression analysis. In this test system, ID_{50} values

of th compounds (16) and (18) were as follows (Table 1). The compounds (16) and (18) of the present invention showed potent antagonism against leukotriene D_4.

Table 1

LTD_4 antagonism in guinea pig ileum

Test Compound	IC_{50}(M)
Inventive Compound (16)	4.6×10^{-10}
Inventive Compound (18)	3.4×10^{-10}

Test Example 2

(Inhibition test of LTD_4-induced bronchoconstriction)

Under urethane anesthesia (1.5 g/5 ml/kg, i.p.), the trachea cannula and the jugular vein cannula were attached to a male Hartley guinea pig. An respirator was connected to the trachea cannula to carry out artificial respiration with a ventilation amount of 10 ml/kg and a ventilation frequency of 60 times/minute. Propranolol (1 mg/kg), succinylcholine (1 mg/kg, to stop spontaneous respiration) and indomethacin (2 mg/kg) were administered by intravenous injection, respectively 5 minutes, 3 minutes and 2 minutes before the administration of LTD_4. After adjusting the amount of ventilation to an airway pressure of 10 $cmH_2O/\ell/sec$, LTD_4 (4 μg/kg) was administered by intravenous injection to induce bronchoconstriction. Each test compound was administered 1 minute before the LTD_4 injection by dissolving it in polyethyl ne glycol 200 in the case of

intravenous injection or an appropriate period before the LTD_4 injection by suspending it in 0.5% carboxymethyl c llulose (CMC) in the case of oral administration. The bronchoconstriction was expressed as a percentage of the maximum reaction obtained by clamping the trachea, and the inhibition percentage was calculated from the peak contraction percentage in the test compound-administered group, using LTD_4-induced peak contraction percentage in a solvent-administered group as the control, based on the following formula (K. Goto *et al.*, *Japan J. Pharmacol.*, 30: 537 - 547, 1980).

Inhibition percentage (%) =

100 - (peak bronchoconstrictuion in test compound-administered group/peak bronchoconstriction in control group) × 100

Duration of inhibitory effect of each test compound on the bronchoconstriction in guinea pigs was measured by orally administering at a dose 10 mg/kg. In this test system, the compound (16) inhibited the bronchoconstriction by 85% even after 24 hours administration (Table 2). Also, 50% inhibition dose (ID_{50}) of the inventive compound (16) calculated by linear regression line analysis was found to be 0.025 (mg/kg).

Table 2

Inhibitory eff ct of test compound on LTD_4-induced bronchoconstriction

Test Compound	Inhibition (%) 4 hr	12 hr	24 hr
Inventive Compound (16), 10 mg/kg (p.o.)	100 ± 0	97 ± 4	85 ± 6

Test Example 3

(Light stability test)

Each test compound was dissolved in methanol to a final concentration of 10 μg/ml and filtered through a membrane filter. This solution was dispensed in 3 ml portions into 5 ml capacity transparent glass sample tubes and used as test samples. One tube was shaded to be used as a control, and the other tube was laid by its side and exposed to light (a fluorescent lamp: 1,000 luxes x hour). Under a shaded condition, each compound was subjected to a reverse phase liquid chromatography to obtain its peak area from which the residual ratio was calculated based on a formula described in the following. Analytical conditions for the liquid chromatography are as follows. A column UG-120 (4.6 mmø x 250 mm; manufactured by Shiseido Co., Ltd.) was used for the analysis, and a solution of 0.01% trifluoroacetic acid aqueous solution:methanol = 2:1 (v/v) was used in the mobile phase. A UV detector was used for the detection, with the detection wave lengths shown in Table 3.

Residual ratio (%) = p ak area of light-irradiated sample/peak area of shaded sample × 100

As the results of the light stability test, residual ratios of double bond compounds [(E)-4-((3-(2-(4-cyclobutyl-2-thiazolyl)ethenyl)phenyl)amino)-2,2-diethyl-4-oxobutyric acid (Ro 24-5913) and (E)-2-((3-(2-(4-cyclobutyl-2-thiazolyl)-ethenyl)phenylamino)-2-oxoethyl)benzoic acid] were found to be 55.5% and 56.4%, respectively, while both of the inventive compounds (16) and (18) as triple bond compounds showed 100% residual ratio with no formation of decomposed fragments (Table 3).

Table 3

Light stability test in liquid state
(fluorescent lamp: 1,000 luxes 3 hours)

Test Compound	Residual Ratio (%)	Detection Wave
Inventive Compound (16)	100.3	312 nm
Inventive Compound (18)	100.9	312 nm
Ro 24-5913	55.5	240 nm
Compound P	56.4	235 nm

(Ro 24-5913):

(E)-4-[[3-[2-(4-cyclobutyl-2-thiazolyl)ethenyl]-phenyl]amino]-2,2-diethyl-4-oxobutyric acid

Compound P:

(E)-2-[2-[3-[2-(4-cyclobutyl-2-thiazolyl)ethenyl]-phenylamino]-2-oxoethyl]benzoic acid

Test Exampl 4

(Toxicity test)

A test compound (the inventive compounds (16) and (18)) was orally administered to 5 five-week-old male rats of Slc:SD line in a dose of 50 mg/kg and 250 mg/kg, and the survival condition was observed for 14 days. The results obtained are shown in Table 4 below.

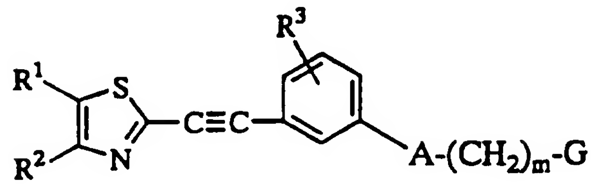
Table 4

Test Compound	Dose (mg/kg)	Mortality*
Inventive Compound (16)	50	0/5
Inventive Compound (18)	50	0/5
Inventive Compound (16)	250	0/5
Inventive Compound (18)	250	0/5

*: Mortality, the number of deaths/individuals used.

CLAIM

1. A compound represented by formula (1) or a salt thereof:



(1)

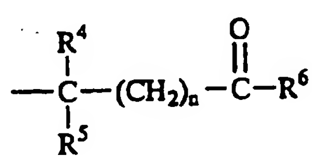
wherein R^1 and R^2 independently represent a hydrogen atom, a halogen atom, an alkyl group which may have a substituent or a cycloalkyl group which may have a substituent, or R^1 and R^2 may together form a ring;

R^3 represents a hydrogen atom, a hydroxyl group, a halogen atom, an alkyl group which may have a substituent, an alkoxyl group which may have a substituent, a carboxyl group or an alkoxycarbonyl group which may have a substituent;

A represents a group -NHCO-, a group -CONH- or a group $-NHSO_2-$;

m is an integer of 0 to 3; and

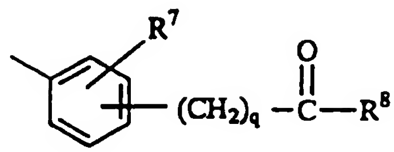
G is a group represented by the forllowing formula (2) or (3):



(2)

wherein R^4 and R^5 independently represent a hydrogen atom or an alkyl group which may have a substituent, or R^4 and R^5 may together form a ring; n is an integer of 0 or 1; and R^6 represents a hydroxyl group or an

alkoxyl group which may have a substituent, or



(3)

wherein R^7 represents a hydrogen atom, a hydroxyl group, a halogen atom, an alkyl group which may have a substituent, an alkoxyl group which may have a substituent, a cyano group, a nitro group, a carboxyl group or an alkoxycarbonyl group which may have a substituent; q is an integer of 0 or 1; and R^8 represents a hydroxyl group or an alkoxyl group which may have a substituent.

2. The compound or a salt thereof according to claim 1, wherein R^2 in the formula (1) is an alkyl group which may have a substituent or a cycloalkyl group which may have a substituent.

3. The compound or a salt thereof according to claim 1 or 2, wherein R^1 in the formula (1) is a hydrogen atom.

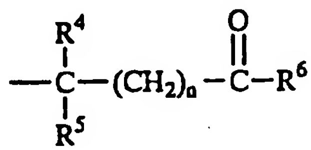
4. The compound or a salt thereof according to any one of claims 1 to 3, wherein R^3 in the formula (1) is a hydrogen atom.

5. The compound or a salt thereof according to any one of claims 1 to 4, wherein A in the formula (1) is a group -NHCO-.

6. The compound or a salt thereof according to any one

of claims 1 to 5, wherein m in the formula (1) is 1.

7. The compound or a salt thereof according to any one of claims 1 to 6, wherein G in the formula (1) is a group represented by formula (2):



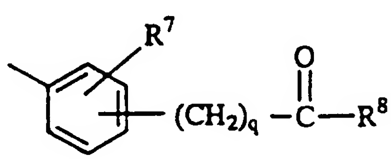
(2)

wherein R^4, R^5, R^6 and n are as defined in the foregoing.

8. The compound or a salt thereof according to claim 7, wherein R^4 and R^5 in the formula (2) independently represent a hydrogen atom or an alkyl group having 1 to 5 carbon atoms which may have a substituent.

9. The compound or a salt thereof according to claim 7 or 8, wherein n in the formula (2) is 0 and R^6 therein is a hydroxyl group.

10. The compound or a salt thereof according to any one of claims 1 to 6, wherein G in the formula (1) is a group represented by formula (3):



(3)

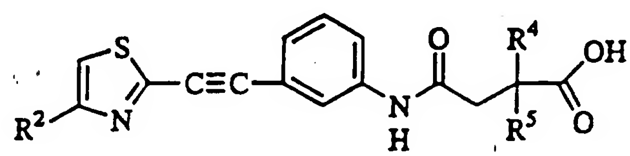
wherein R^7, R^8 and q are as defined above.

11. The compound or a salt thereof according to claim 10, wherein R^7 in the formula (3) is a hydrogen atom.

12. The compound or a salt thereof according to claim 10 or 11, wherein the group $-(CH_2)_q-CO-R^8$ in the formula (3) is linked to the ortho position of the phenyl group.

13. The compound or a salt thereof according to any one of claims 10 to 12, wherein R^8 in the formula (3) is a hydroxyl group.

14. A compound represented by formula (4) or a salt thereof:

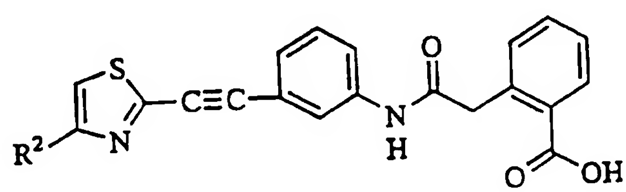


(4)

wherein R^2 represents an alkyl group which may have a substituent or a cycloalkyl group which may have a substituent; and R^4 and R^5 independently represent a hydrogen atom or an alkyl group having 1 to 3 carbon atoms which may have a substituent.

15. The compound according to any one of claims 1 to 9 and 14, or salts thereof or optical isomers thereof, wherein R^4 and R^5 are different from each other.

16. A compound represented by the following formula (5) or a salt thereof:



(5)

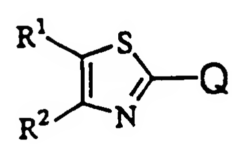
wherein R^2 represents an alkyl group which may have a substituent or a cycloalkyl group which may have a substituent.

17. 4-[[3-[2-(4-Cyclobutyl-2-thiazolyl)ethynyl]-phenyl]amino]-2,2-diethyl-4-oxobutyric acid and 4-[[3-[2-(4-isopropyl-2-thiazolyl)ethynyl]phenyl]amino]-2,2-diethyl-4-oxobutyric acid, or a salt thereof.

18. 2-[2-[3-[2-(4-Cyclobutyl-2-thiazolyl)ethynyl]-phenylamino]-2-oxoethyl]benzoic acid and 2-[2-[3-[2-(4-isopropyl-2-thiazolyl)ethynyl]phenylamino]-2-oxoethyl]benzoic acid, or a salt thereof.

19. A compound selected from the group consisting of 2-[[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenylamino]-carbonyl]benzoic acid, 2-[[[3-[2-(4-cyclobutyl-2-thiazolyl)-ethynyl]phenyl]carbonyl]amino]benzoic acid and 4-[[3-[2-(4-cyclobutyl-2-thiazolyl)ethynyl]phenylamino]sulfonyl]benzoic acid, or a salt thereof.

20. A compound represented by formula (6) or a salt thereof:



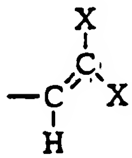
(6)

wherein R^1 and R^2 are as defined above, and Q is a group represented by formula (7), (8), (9), (10), (11), (12), (13) or (14):

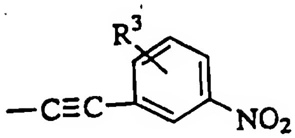
$-CO_2Et$ (7),

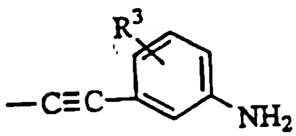
$-CH_2OH$ (8),

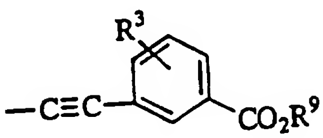
$-CHO$ (9),

 (10),

$-C \equiv C-H$ (11),

 (12),

 (13), and

 (14)

wherein X represents a halogen atom other than fluorine, R^3 is as defined above and R^9 represents a hydrogen atom or an alkyl group which may have a substituent.

21. An allergic disease treating drug which contains as active ingredient the compound of any one of claims 1 to 19 or a salt thereof.

22. A leukotriene antagonist which contains as active ingredient the compound of any one of claims 1 to 19 or a salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 96/01079

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/28 C07D277/30 A61K31/425 C07D277/56 C07D277/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 577 003 (HOFFMANN LA ROCHE) 5 January 1994 see claims ---	1-10,21,22
Y	US,A,5 288 751 (BROOKS DEE W ET AL) 22 February 1994 see column 8, line 30 - column 12, line 7; claims ---	1-10,21,22
Y	EP,A,0 219 436 (MITSUBISHI CHEM IND) 22 April 1987 see claims ---	1-10,21,22
Y	EP,A,0 355 353 (HOFFMANN LA ROCHE) 28 February 1990 see claims --- -/--	1-10,21,22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 1996	05.07.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HELVETICA CHIMICA ACTA, vol. 29, 1945, BASEL CH, pages 924-925, XP002006764 H.ERLENMEYER ET AL: "Zur Kenntnis der Thiazol-2-carbonsäure" see the whole document	20
X	US,A,2 341 687 (WILLIAM ROBERT BOON) 15 February 1944 see example 1	20
X	HELVETICA CHIMICA ACTA, vol. 31, no. 2, 1948, BASEL CH, pages 652-665, XP002006765 MAX ERNE ET AL: "über die Kondensation von 4,5-Dimethylthiazol und 5-Methylthiazol mit aldehyden" see the whole document	20
X	HELVETICA CHIMICA ACTA, vol. 29, no. 7, 1946, BASEL CH, pages 1957-1959, XP002006766 H.ERLENMEYER ET AL: "Über die Reaktionfähigkeit der Methylgruppe im 5-Methyl-thiazol" see the whole document	20
X	HELVETICA CHIMICA ACTA, vol. 36, no. 7, 1953, BASEL CH, pages 1842-1845, XP002006767 L.HERZFELD ET AL: "Über das thiazol-Isostere der Fusarinsäure" see the whole document	20
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 74, no. 24, 20 December 1952, DC US, pages 6260-6262, XP002006768 RAYMOND P. KURKJY ET AL: "The preparation of thiazole Grignard reagents and thiazolyllithium compounds" see table I Compound 15	20
X	CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 35, no. 2, February 1987, TOKYO JP, pages 823-828, XP002006769 TAKAO SAKAMOTO ET AL: "Palladium-catalysed reactions of terminal acetylenes and olefins with halo-1,3-azoles" see the whole document	20

-/--

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE CHEMICAL SOCIETY, 1949, LETCHWORTH GB, pages S106-S111, XP002006770 D.J.BROWN ET AL: "The preparation of potential analgesic compounds" see page S110	20
X	CHEMISCHE BERICHTE, vol. 90, 1957, WEINHEIM DE, pages 2372-2378, XP002006771 HANS BEYER ET AL: "Über Thiazole,XXXV.Eine neue Synthese von Thiazol-2-aldehyden" see the whole document	20
X	CHEMICAL ABSTRACTS, vol. 32, no. 5, 10 March 1938 Columbus, Ohio, US; abstract no. 1699, HEISABURU KONDO ET AL: "Activity of methyl side chains in the thiazole ring" page 1699; column 1; XP002006772 see abstract & J.PHARM.SOC.JAPAN, vol. 57, 1937, pages 909-919,	20
X	CHEMICAL ABSTRACTS, vol. 52, no. 11, 10 June 1958 Columbus, Ohio, US; abstract no. 9143b, FRIEDRICH ASINGER ET AL: "VII.Dehydrogenation of delta3-thiazolines with the formation of thiazoles" page 9143; column 1; XP002006773 see abstract & LIEBIGS,ANNALEN DER CHEMIE, vol. 610, 1957, pages 49-56,	20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 96/01079

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0577003	05-01-94	US-A-	5273986	28-12-93
		AU-B-	4156293	06-01-94
		BR-A-	9302737	08-02-94
		CA-A-	2099295	03-01-94
		CN-A-	1087086	25-05-94
		CZ-A-	9301334	19-01-94
		HU-A-	72747	28-05-96
		JP-A-	6080654	22-03-94
		NO-A-	932399	03-01-94
		NZ-A-	247988	27-11-95
		PL-A-	299544	21-02-94
		US-A-	5399702	21-03-95
		ZA-A-	9304603	05-01-94
US-A-5288751	22-02-94	AU-B-	5666094	08-06-94
		CA-A-	2136077	26-05-94
		EP-A-	0667855	23-08-95
		JP-T-	8503200	09-04-96
		WO-A-	9411342	26-05-94
EP-A-0219436	22-04-87	JP-C-	1797266	28-10-93
		JP-B-	5007386	28-01-93
		JP-A-	62142168	25-06-87
		AU-B-	603343	15-11-90
		AU-B-	6393086	30-04-87
		CA-A-	1326034	11-01-94
		DE-D-	3689436	03-02-94
		DE-T-	3689436	14-04-94
		DK-B-	169128	22-08-94
		SU-A-	1554763	30-03-90
		US-A-	4902700	20-02-90
EP-A-0355353	28-02-90	US-A-	5001140	19-03-91
		AU-B-	626308	30-07-92
		AU-B-	3828089	18-01-90
		BG-B-	60765	29-02-96
		CA-A-	1333906	10-01-95
		DE-D-	68913856	21-04-94
		DE-T-	68913856	20-10-94
		ES-T-	2052825	16-07-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 96/01079

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0355353		FI-B- 93953	15-03-95
		JP-A- 2069468	08-03-90
		JP-B- 7037454	26-04-95
		NO-B- 175476	11-07-94
		PT-B- 91179	01-03-95
		SI-A- 8911402	31-12-94
US-A-2341687	15-02-44	NONE	